

PEDIATRIC
SELF-ASSESSMENT PROGRAM

PedSAP



2017 • BOOK 1
**RESEARCH AND STUDY
DESIGN IN PEDIATRICS**

Series Editors
Marcia L. Buck, Pharm.D., BCPPS, FCCP, FPPAG
Kalen B. Manasco, Pharm.D., BCPS

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Director of Professional Development: Nancy M. Perrin, M.A., CAE
Associate Director of Professional Development: Wafa Y. Dahdal, Pharm.D., BCPS
Recertification Project Manager: Edward Alderman, B.S., B.A.
Medical Editor: Kimma Sheldon, Ph.D., M.A.
Information Technology Project Manager: Brent Paloutzian, A.A.S.

For ordering information or questions, write or call:

Pediatric Self-Assessment Program
American College of Clinical Pharmacy
13000 W. 87th St. Parkway
Lenexa, KS 66215-4530
Telephone: (913) 492-3311
Fax: (913) 492-4922
E-mail: accp@accp.com

Library of Congress Control Number: 2016955603
ISBN-13: 978-1-939862-43-3 (PedSAP 2017 Book 1, *Research and Study Design in Pediatrics*)

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To cite PedSAP properly:

Authors. Chapter name. In: Buck ML, Manasco KB, eds. Pediatric Self-Assessment Program, 2017 Book 1. *Research and Study Design in Pediatrics*. Lenexa, KS: American College of Clinical Pharmacy, 2017:page range.



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Pediatric
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TABLE OF CONTENTS

Research and Study

Design in Pediatrics I	1
Research and Study Design In Pediatrics I Panel	3

Ethical Considerations in Pediatric Research

By Anthony T. Podany, Pharm.D.

Introduction	7
History of Human Subjects Research	8
Ethical Considerations	9
Informed Consent and Assent	9
Ethical Study Design in the Pediatric Patient Population	11
Challenges in Conducting Pediatric Research	12
Conclusion	14
References	14
Self-Assessment Questions	15

Study Design in Pediatrics

By Mary Jayne Kennedy, Pharm.D., DABCP

Introduction	21
When Is a Pediatric Study Necessary?	22
Common Types of Pediatric Pharmacology Studies	25
General Considerations in Pediatric Study Design	26
Conducting Pediatric Studies	31
Interpreting and Analyzing Data from Pediatric Studies	32
Overcoming the Challenges of Pediatric Research	33
Conclusion	36
References	36
Self-Assessment Questions	38

Database Research in Pediatrics

By Donald Klepser, Ph.D.; and Gary L. Cochran, Pharm.D., S.M.

Introduction	43
Database Research	44
Database Research Study Considerations	46
Examples of Pediatric Databases	48
Conclusion	49
References	49
Self-Assessment Questions	51

Clinical and Practice Updates I	55
Clinical and Practice Updates I Panel	57

Recorded Webcast: Pediatric Study Design

By Mary Jayne Kennedy, Pharm.D., DABCP

Link to Recorded Webcast	61
References	62
Self-Assessment Questions	63

Interactive Case: Developing and Adopting Novel Therapies in the NICU

By Peter Gal, Pharm.D., FCCP, FASHP, FPPAG

Link to Interactive Case	65
References	66
Self-Assessment Questions	70

Recorded Webcast: Medical Records Research

By Christopher Shaffer, Pharm.D., M.S., BCPS

Link to Recorded Webcast	73
References	74
Self-Assessment Questions	75

A Message From the Editors

Welcome to the Pediatric Self-Assessment Program (PedSAP), a new recertification component for the Board Certified Pediatric Pharmacy Specialist (BCPPS). ACCP has a long tradition of offering the best products for continuing pharmacy education and pharmacotherapy specialist certification. PedSAP continues that tradition by providing the latest in evidence-based information for the practitioner or clinician working with this special population.

In designing this series, the primary goal was to provide updates that would improve clinical pharmacy practice and patient outcomes. The process began with a careful review of the content outline developed by the Board of Pharmacy Specialties for the Pediatric Pharmacy Specialty Certification Examination. The 2017–2018 PedSAP chapters will therefore cover the domains of patient management; practice management; information management and education; and public health and patient advocacy. Specific content for individual releases in this series was organized on the basis of the systems and patient care problems that might be expected of the BCPPS. Finally, calls went out to recruit faculty panel chairs, authors, and reviewers committed to this new specialty and to the board certification process.

The presentation of information, and its incorporation into practice, was also given careful consideration. In a departure

from ACCP's other self-assessment programs, PedSAP modules come in two formats: (1) the traditional review chapters; and (2) Clinical and Practice Update modules that incorporate new learning formats such as recorded webinars and HTML pages. These new learning formats are hoped to speed the dissemination of new clinical information and satisfy the learning preferences of a wider audience.

Some things have not changed: inside this PedSAP book, you will find user-friendly formatting as well as graphic elements such as patient care scenarios (demonstrating the application of concepts), treatment algorithms, descriptions of pivotal studies that may change practice, and summative practice points. All releases in this series are available electronically, enhancing the portability of this product. Prominent in each chapter are hyperlinks to reference sources, assessment tools, guidelines and resources, data compilers such as PubMed, and even informational videos. Our hope is that this depth of information, ease of access, and emphasis on clinical application will have an immediate and positive impact on the care of pediatric patients.

We very much appreciate the efforts of all the faculty panel chairs, authors, and reviewers who lent their time, energy, and expertise to this new series.

Marcia L. Buck and Kalen B. Manasco, series editors

Research and Study Design in Pediatrics I

Research and Study Design In Pediatrics I Panel

Series Editors:

Marcia L. Buck, Pharm.D., BCPPS, FCCP, FPPAG

Clinical Coordinator
University of Virginia Children's Hospital
Professor
Department of Pediatrics
University of Virginia School of Medicine
Clinical Professor
Virginia Commonwealth University School of Pharmacy
Department of Pharmacy Services
University of Virginia Health System
Charlottesville, Virginia

Kalen B. Manasco, Pharm.D., BCPS

Clinical Associate Professor
Department of Clinical and Administrative Pharmacy
University of Georgia College of Pharmacy
Augusta, Georgia

Faculty Panel Chair:

Christopher Shaffer, Pharm.D., M.S., BCPS

Associate Dean
University of Nebraska Medical
Center College of Pharmacy
Assistant Professor
Department of Pharmacy Practice and Pediatrics
University of Nebraska Colleges of
Pharmacy and Medicine
Director, Pediatric Precision Medicine Program
Children's Hospital and Medical Center
University of Nebraska Medical Center
Omaha, Nebraska

Ethical Considerations in Pediatric Research

Author

Anthony T. Podany, Pharm.D.

Assistant Professor
Associate Director, Pediatric and Adolescent Pharmacology Research Unit
Department of Pharmacy Practice
University of Nebraska Medical Center
Omaha, Nebraska

Reviewers

Emily L. Rowe, Pharm.D., M.S., BCPS, BCPPS

Senior Clinical Pharmacy Specialist
Pharmacy Department
Floating Hospital for Children at Tufts Medical Center
Boston, Massachusetts

Margaret Burke, Pharm.D., BCPPS

Medical Writer
Precision Medical Writing, LLC
Manchester, Connecticut
Clinical Pharmacist
Pharmacy Department
Connecticut Children's Medical Center
Hartford, Connecticut

Study Design in Pediatrics

Author

Mary Jayne Kennedy, Pharm.D., DABCP

Professor and Chair
Department of Clinical Sciences
High Point University School of Pharmacy
High Point, North Carolina

Reviewers

Mary Ryan, Pharm.D., BCPPS

Investigational Pharmacist
Department of Pharmacy, Research Pharmacy Services
Oregon Health and Sciences University
Portland, Oregon

Melissa Ray, Pharm.D., BCPS, BCPPS

Clinical Pharmacist III
United Health Group
Tampa, Florida
Clinical Assistant Professor of Pharmacy Practice
University of Florida College of Pharmacy
Gainesville, Florida

Database Research

Authors

Donald Klepser, Ph.D.

Associate Professor
Department of Pharmacy Practice
University of Nebraska Medical Center
Omaha, Nebraska

Gary L. Cochran, Pharm.D., S.M.

Associate Professor
Department of Pharmacy Practice
University of Nebraska Medical Center
Omaha, Nebraska

Reviewers

Drew Roberts, Pharm.D., Ph.D.

Assistant Professor of Pharmacy Services
Creighton University School of Pharmacy
and Health Professions
Omaha, Nebraska

Courtney Sutton, Pharm.D., BCPPS

Pediatric Clinical Pharmacy Specialist
Pharmacy Department
Williamson Medical Center
Franklin, Tennessee

Brent A. Hall, Pharm.D., BCPPS

Senior Pharmacist, Pediatrics
UC Davis Children's Hospital
Sacramento, California
Assistant Clinical Professor
UCSF School of Pharmacy
San Francisco, California

The American College of Clinical Pharmacy and the authors thank the following individuals for their careful review of the Research and Study Design in Pediatrics I chapters:

Nicola G. Dahl, Pharm.D.

Medical Writer
Kanab, Utah

Mary Wun-Len Lee, Pharm.D., FCCP, BCPS

Vice President and Chief Academic Officer
Pharmacy and Optometry Education
Midwestern University
Professor of Pharmacy Practice
Midwestern University
Chicago College of Pharmacy
Downers Grove, Illinois

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

Consultancies: Mary Jayne Kennedy (NHLBI, Guilford County Public Health); Donald Klepser (Viiv, Force Diagnostics); Melissa Ray (Pharmacist's Letter, Hospital Pharmacist's Letter)

Stock Ownership:

Royalties: Donald Klepser (NACDS)

Grants: Gary L. Cochran (USDHHS Office of the National Coordinator for HIT); Donald Klepser: (NACDS, NACDS Foundation, Roche Diagnostics, USDHHS Office of the National Coordinator for HIT); Drew Roberts (Academy Health, NIH)

Honoraria:

Other:

Nothing to disclose: Manal M. Abou Elkheir; Margaret Burke; Brian J. Cowles; Melissa Gabriel; Peter Gal; Brent A. Hall; Anthony T. Podany; Monica A. Puebla; Emily L. Rowe; Mary Ryan; Christopher Shaffer; Kathleen Sprott; Courtney Sutton; Brandy Zeller

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2215 Constitution Avenue NW

Washington, DC 20037

(202) 429-7591

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ACPE test deadline: 11:59 p.m. (Central) on January 14, 2020.

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Ethical Considerations in Pediatric Research

By Anthony T. Podany, Pharm.D.

Reviewed by Emily L. Rowe, Pharm.D., M.S., BCPS, BCPPS; and Margaret Burke, Pharm.D., BCPPS

LEARNING OBJECTIVES

1. Apply the ethical principles described in the Belmont Report.
2. Demonstrate the concepts of beneficence, justice, and respect for persons as they relate to pediatric research.
3. Discover study design issues that are implicated by the inclusion of pediatric subjects.
4. Evaluate challenges to conducting research in pediatric populations.

ABBREVIATIONS IN THIS CHAPTER

CFR	Code of Federal Regulations
IRB	Institutional review board
NI	Noninferiority

[*Table of other common abbreviations.*](#)

INTRODUCTION

The conduct of research in pediatric subjects is crucial to optimizing clinical care in this diverse patient population. Although the demand for pediatric research remains high, the logistical implementation is complex. Many factors have led to a lack of pediatric research, including lack of agreed-on end points, informed consent issues, and the general perception that pediatric patients are vulnerable study subjects. This perceived vulnerability of children is based on several factors: (1) their decision-making capacity may be immature, (2) their lives are still subject to the authority of others, (3) their underlying dissent may be masked for fear of upsetting authority figures, and (4) their rights and interests may be undervalued by society.

To ensure that pediatric patients are provided the best clinical care, it is important that thoughtful, efficient research be conducted that has the scientific merit to answer important clinical questions. The fundamental challenge to pediatric research is risk: what is the risk of conducting (or not conducting) the research, and who has the right to decide the level of risk exposure to the child? What “say” does a child have in agreeing to participate in research? What “say” does the legal guardian have in agreeing for a child to participate in research? What is the ultimate goal of the research? Finally, does the goal of the research justify the risks associated with the study?

This chapter outlines the ethical factors affecting the successful conduct of pediatric research. Ethical considerations and their relationship within the context of informed consent and assent are discussed. The discussion of clinical research design focuses on ethical challenges inherent to researchers, especially those unique to pediatric patients. Finally, additional confounders to pediatric research, such as compensation and the role of the pharmaceutical industry, are discussed.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of terms associated with conducting clinical research
- Basic anatomic and physiologic differences between adults and adolescents
- Fundamental principles of medical ethics

[Table of common pediatric laboratory reference values.](#)

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Caldwell PH, Murphy SB, Butow PN, et al. [Clinical trials in children](#). *Lancet* 2004;364:803-11.
- Fleischman AR. [Ethical issues in neonatal research involving human subjects](#). *Semin Perinatol* 2016;40:247-53.

HISTORY OF HUMAN SUBJECTS RESEARCH

The exploitation of subjects by researchers has a long and dark history. One of the most graphic exploitations was that conducted by the Nazi regime during World War II. Prisoners of war were forced to participate in research experiments against their will, often with no benefit. After the war, during the trials in Nuremberg, German physicians were charged with crimes against humanity for experiments in the concentration camps that led to murders, tortures, and other atrocities. The Nuremberg trials outlined areas in which permissible medical experiments can be conducted, with the findings ultimately becoming the Nuremberg Code.

Several high-profile research studies showing questionable ethics occurred after the Nuremberg Code was established. The most famous was the U.S. Public Health Service “Study of Untreated Syphilis in Negro Males,” often called the Tuskegee Syphilis Study. African American males who had contracted syphilis were prohibited from knowing their infection status as well as from receiving appropriate treatment so that researchers could track the natural course of the disease. This study occurred when a known treatment for syphilis was available. In 1972, public awareness of the study led to an outcry and eventual study discontinuation.

Unfortunately, lapses in ethical judgment are not limited to adult subjects. History has shown cases in which the interest of the child’s legal guardian conflicted with the best interest of the child. For example, the cases surrounding Willowbrook State School showed that legal guardians allowed their child to be enrolled in questionable hepatitis studies to ensure

their child would be enrolled in the school for mentally handicapped children. Although the legal guardians knew it was questionable to allow their child to participate in this study, they feared that declining participation would not allow their child to be enrolled in Willowbrook, a notoriously difficult school to gain admittance to. The Willowbrook example shows how the rights of children can be compromised by guardians and health care communities alike.

A second example of ethical wrongdoing in pediatric subjects can be extracted from the human radiation experiments conducted at the Walter E. Fernald Developmental Center in Waltham, Massachusetts. In these experiments, young male wards of the institution were exposed to trace levels of radioactive calcium and iron in an attempt to discern issues of mineral absorption. Parents of the children enrolled in the studies were given incomplete information regarding the study when providing their consent. The parents were never told the children would be receiving any radiation, whereas the children were led to believe they were simply joining a science club. The experiments raised important issues of what is truly “informed consent” and whether institutionalized children should ultimately be able to enroll in clinical research, given that they are by nature a vulnerable population.

The U.S. Senate Committee on Labor and Public Welfare met in 1973 to address human experimentation as a result of the public outcry associated with the Tuskegee Syphilis Study and the Willowbrook cases. In 1974, the National Research Act was passed by Congress. The National Research Act was instrumental in two important acts: (1) the establishment of the National Commission, which would develop the ethical principles associated with human subjects research; and (2) the requirement for institutional review boards (IRBs). About the same time that the National Research Act was passed, the Public Health Service implemented “Regulations for the Protection of Human Subjects of Biomedical and Behavioral Research.” These regulations (45 Code of Federal Regulations [CFR] 46) continue to serve as the basis for federal-specific requirements in the conduct of human subjects research (Services 2005).

The National Commission meeting occurred in 1975–1978 to deliberate regulations governing human subjects research. Topics ranged from IRB governance to research in vulnerable subjects (e.g., fetuses, prisoners, children, and the developmentally delayed). As part of these proceedings, the committee met in 1976 at the Belmont Conference Center to discuss the basic ethical principles that would serve as the framework for human subjects research. The findings of the committee (the Belmont Report) were incorporated into the National Commission’s final report in 1979. The NIH published guidelines in 1998 titled “Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.” The basis for these guidelines stemmed from the lack of clinical studies involving pediatric patients. To receive NIH funding for a clinical drug study, children must be included in research

protocol unless (1) the research is not applicable to children, (2) the knowledge sought is already available in children (or will be obtained from a currently funded study), (3) an age-specific separate study is warranted and preferred, or (4) insufficient data exist in adults to determine whether children are at potential risk. The NIH guidelines continue to state that including children in NIH-sponsored studies should follow the regulations of 45 CFR 46 (Services 2005; National Commission 1978).

ETHICAL CONSIDERATIONS

The Belmont Report identified three ethical principles that serve as a framework for human subjects research: beneficence, justice, and respect for persons. One principle is no more or less important than the others; rather, all three must be considered when conducting research. Under some circumstances, all three principles may be in conflict with one another, and the researcher must choose the appropriate direction that best answers the scientific question. Applying these principles can be challenging in both adult and pediatric subjects. However, unique differences in pediatric subjects will be discussed in the sections that follow.

Beneficence

Beneficence is the ethical principle that is founded in kindness and acts of charity. It is a moral obligation to act for the other's benefit, help them further their interest, and prevent or remove possible harm (*primum non nocere*). As it applies to health care and biomedical research, it is often summarized as "do no harm." In pediatric research, it is important that research does not exploit the vulnerability of minors who may be unable to give true assent for study participation. Therefore, the researcher must ensure that the research question is scientifically sound and that no "unnecessary" harm is done to the study subject. A key aspect of harm as it relates to research is "risk," which serves as a basis for research review by the IRB. As discussed later in the chapter, the IRB assesses the risk to the research subject and any potential benefit to the patient or future patients. There is considerable debate regarding the role of beneficence for a patient when the patient will not receive any direct benefit from the research. In the adult population, it is widely accepted that a researcher can risk a small level of harm to the research subject if the subject willingly consents to treatment that will benefit humanity. The ability of a child to comprehend the risk in the larger picture of human health and the child's willingness to assent to such risk are subject to significant research debate.

Justice

Justice is the ideal distribution of risk and benefits throughout a population when conducting research. The selection of subjects should be equitable, and vulnerable subjects should not be exploited for the benefit of the general population. The inclusion and exclusion of subjects in research protocols

should be based on a valid scientific question and not based on discriminatory factors or ease of enrollment. One aspect of biomedical research is to determine whether an intervention improves, does not improve, or has no effect on a pathophysiologic condition. The principle of justice states that individuals within a population should have equitable access to the potential benefits of the intervention and share in the potential risks. Factors that may disrupt the equitable distribution of participation include demographic differences (e.g., minority and wealth differences, primary language), mental status, and coercion by investigators based on financial incentives. This last aspect is of particular relevance in the pediatric population because of concerns that investigators may coerce children to provide assent because of financial incentives such as a gift card to a toy store or fast food restaurant. The value of such financial incentives is often reviewed by IRBs to ensure that it is consistent with community standards and not a source of potential enticement.

Respect for Persons

The third ethical principle of "respect for persons" can underscore an important challenge in pediatric research: paternalism versus autonomy. Autonomy is the belief that a rational individual has the capacity to make an informed decision. Paternalism, however, is the belief that an individual is incapable of making an informed decision and that a surrogate must make the decision in the best interest of the individual. A classic example of the struggle of autonomy versus paternalism lives in the house of every teenager. A key tenet in human subjects research is the subject's ability to make an informed decision regarding whether to participate, given the perceived risk. The autonomous decision of a coherent adult is obvious, but at what point can an autonomous decision be made by a child? Do children have the ability to make autonomous decisions, or does a paternalistic decision need to be made in the best interest of the child? Societies perceive "adulthood" (or the ability to make autonomous decisions) according to a variety of factors such as age, sexual development, and schooling. In the United States, the "age of majority" is 18 years in most states, with 19 years in others. It is widely accepted that a child can make an autonomous decision at this age.

INFORMED CONSENT AND ASSENT

The informed consent process is based on the ethical principle "respect for persons." As discussed in the National Commission's 1979 report, research subjects "shall be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied." The standards of informed consent include that (1) information should be provided to the potential subject such that they can decide whether to participate; (2) the information should be presented in such a way that it can be easily understood; and (3) the potential subject should understand that consent is voluntarily given and the

individual is free to withdraw at any time. The applications of these standards to the pediatric patient can be challenging. For example, what is the appropriate way to ensure that a 10-year-old understands the information being presented by the researcher? Thus, it becomes imperative that researchers work with the child's guardian to meet the informed consent standards to the best of their ability. Informed consent is typically a legal document; thus, the age required to give consent is the age at which one is considered an adult. In the United States, the age is typically 18 years. Written assent is often required from teenagers in addition to consent from parents; some IRBs have required the use of consent forms for older teenagers (16–17 years) whereby both the teen and the parent/guardian ascertain consent. The National Commission's report "Additional Protections for Children as Research Subjects" was published in 1977 and serves as the basis for regulations 45 CFR 46 (Subpart D) (Jonsen 1978).

Overview of Risk Categories

The regulations contained within 45 CFR 46 describe the various levels of risks in research involving children. These risks are classified in levels according to the risk-benefit ratio provided directly to the child. The greater the risk-benefit ratio, the more protections that are required for the child. These levels were implemented in sections 45 CFR 46.404, 46.405, 46.406, and 46.407 of Subpart D of the Health and Human Services regulations. A summary of the pediatric research risk is provided in Table 1-1.

Minimal risk is often defined as harm or discomfort similar to that encountered in everyday life during physical or psychological examinations or tests. Thus, research activities are compared with the likelihood of minimal risk or greater. Risk is further delineated regarding whether the subject has the prospect of direct benefit by participating in the study (see Table 1-1). Consent or assent can be waived according to 45 CFR 46.116(d) when subject information is collected but de-identified and no correlation exists between the information presented and an individual subject because the risk is considered negligible.

Institutional review boards are responsible for assessing the levels of risk in conjunction with the principal investigator. This assessment is done after reviewing the study protocol. A common misconception is that the IRB is responsible for research study design when, in fact, the IRB's primary responsibility is to protect the study subject. It can be implied that a poorly designed research study does not answer the research question and places the subject at unnecessary risk. Regardless, it remains the IRB's primary focus to protect the rights of the research subject through the assessment of risk, the appropriate execution of informed consent, and the appropriate review and execution of assent.

Informed Consent

Informed consent is the legal permission that a patient voluntarily agrees to participate in a research study. Informed consent must be signed by the legal guardian(s) of the child

Table 1-1. Risk Categories in Pediatric Research

45 CFR 46 Code	Descriptor	Examples	Consent
404	Research involving no greater than minimal risk	Venipuncture Chest radiograph Psychological risk Classroom observation	One parent Child assent
405	Research involving greater than minimal risk but presenting the prospect of direct benefit	Shortened course of therapy compared with conventional practice	One parent Child assent
406	Research involving greater than minimal risk and no prospect for direct benefit	Urine catheterization Skin or bone marrow biopsy Radiocontrast with sedation	Both parents Child assent
407	Research otherwise not approvable	Research not approvable by previous sections but presents an opportunity to understand, prevent, or alleviate a serious problem	Both parents Child assent HHS panel of experts
116	Waiver of consent or assent	De-identified patient information for performance improvement or research publication	Not applicable

HHS = Health and Human Services.

with the number of signatures needed, depending on the risk of the research (see Table 1-1). Informed consent must be written in a manner that satisfies the IRB standard that “the information must be provided in a form that is understandable.” An eighth-grade reading level is generally accepted to be appropriate for general adult comprehension. Adults who serve as a child’s legal guardian must sign the informed consent, and this step cannot be delegated to other family members or friends unless legally certified. Children who are wards of the state have additional safeguards because previous exploitations often involved orphans. Regulation 45 CFR 46.409 limits the involvement of wards in research that is greater than minimal risk and without direct subject benefit. In addition, regulations stipulate that children who are wards of the state must be appointed an advocate who has the background and experiences consistent with serving in this capacity.

Informed Child and Adolescent Assent

The concept of informed assent for children is similar to that of obtaining informed consent for adult research subjects. Although informed assent is not legally binding, it remains an ethical cornerstone in that a child or adolescent is giving his or her permission to voluntarily participate as a research subject and understands the risk of doing so to the best of his or her ability. As such, the child/adolescent should be given the rights outlined in Box 1-1.

Assent is generally divided into three categories: children too young to properly give informed assent (neonate to age 6 years), youth assent (children age 7–12 years), and adolescent consent (given to children age 13–18 or 19 years, depending on each state). Children younger than 7 years should be given simple verbal explanation of what the research study entails, what will happen to them, and what they may be asked to do. It is important to document this conversation either on the parental permission form or in the study records.

The youth and adolescent assent forms differ in the scope and context of information provided to the child. The adolescent assent form is slightly more complex than the youth

form. Both assent forms should be brief and study-specific, with subheadings or numeric paragraphs, and contain language that is appropriate to both the child’s development and age. The assent form should have a simple format that is easy to read and, when possible, should be limited to one page.

Children are not required to sign the assent form, but investigators are required to document in the research record that child assent has either been obtained on the parental permission form or retained separately within the study records. It may be necessary to use two assent forms written to accommodate subjects at either end of the age range or to accommodate different maturity levels of the participants.

Even when the researcher and the IRB determine that the children are capable of assenting, the IRB may grant a waiver of the assent requirement in accordance with 45 CFR 46.116(d). This would include when the capability of the child is so limited that he or she cannot reasonably be consulted or the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research. In circumstances such as a child’s dissent, which should normally be respected, the dissent may be overruled by the child’s parents.

Ultimately, the institutional IRB is responsible for determining that appropriate provisions are made in obtaining assent from the child and adolescent. If the IRB determines that a pediatric research subject is capable of providing informed assent, the study protocol must include this information. It is important that researchers work closely with their respective IRB to conduct actions of assent and consent.

ETHICAL STUDY DESIGN IN THE PEDIATRIC PATIENT POPULATION

It is critical in all aspects of research to specifically target the research question. This takes on particular relevance in the pediatric patient population because children have historically been perceived as vulnerable study subjects. Therefore, children should not participate in clinical research unless it is necessary to answer an important scientific question that is pediatric-specific. It is well described that research should be conducted in adults before pediatric patients unless the disease is unique to pediatric patients. This stems from the belief that most adults can assess the risk and benefits of being associated with a study, whereas a child may not fully comprehend the expectations associated with participating in a study.

Inversely, not conducting pediatric research can be equally unethical. If a health care practitioner is forced to make clinical decisions on a case-by-case basis, pediatric patients could be faced with unnecessary harm because of the lack of a cohesive, evidence-based approach that benefits the entire population. Thus, the best way to balance the risk-benefit

Box 1-1. Rights of Pediatric Assent

1. Conducting the process in a manner and location that ensures participant privacy
2. Giving adequate information about the study in a language understandable to the participant
3. Providing adequate opportunity for the participant to consider all options
4. Responding to the participant’s questions
5. Ensuring the participant has understood the information provided
6. Obtaining the participant’s voluntary agreement to participate
7. Continuing to provide information as the participant or research requires

ratio in pediatric research is for the health care practitioner to be aware of confounding factors affecting the risk-benefit ratio as it applies to pediatric research.

Targeting the Research Question

The importance of minimizing risk and maximizing benefit centers on establishing an answerable research question. The question should be direct and based on the concept of clinical equipoise. Clinical equipoise states that a research subject should not be provided inferior treatment by participating in the research study. Therefore, the scientific question must be based on scientific “uncertainty”: the interventions must be perceived as equitable rather than conducting a study with a known inferiority. The nature of the research question should be specific and should clearly enumerate the scientific uncertainty leading to the study design. Therefore, each group (including the control group) should be vetted for ethical and scientific rationale before the research protocol is initiated.

Control Group and Placebo Controls

The choice of an appropriate control group should be based on both scientific and ethical principles. The primary focus should be on using the appropriate comparator to show the safety or efficacy of the intervention. Thus, having an intervention studied versus placebo is often perceived as the ultimate comparator. It is commonly thought that the individuals assigned to the placebo group are receiving inferior treatment, thereby compromising clinical equipoise. However, another option to consider is that the placebo group could be limited to the exposure of a potentially ineffective or toxic intervention. Treatment (or nontreatment) of patent ductus arteriosus (PDA) shows this clinical equipoise. Historically, the standard of care for neonatal PDA was either surgery or pharmacologic treatment with indomethacin or ibuprofen. The research question was raised: What if there was no intervention for PDA and the duct was able to resolve on its own? Although groups of health care practitioners argued that it would be unethical not to intervene, proponents of the research challenged that the pharmacologic treatment could be considered a greater risk than benefit and the study should proceed. Studies showed that the no-intervention group (essentially a placebo group) had better outcomes than the pharmacologic intervention group. This example shows that a perceived intervention may not be clinically advantageous to the placebo group.

Alternatives to Placebo-Controlled Trials

The complexity of the scientific and ethical questions regarding pediatric placebo-controlled studies makes this approach somewhat limited in practice. Thus, investigators have explored a “placebo-like” experience without the scientific and ethical concerns associated with a placebo-controlled trial. A common approach, both in children and adults, is the noninferiority (NI) study. An NI study is intended to show that a new treatment is

no worse than the active control (typically, the current standard of care) by a specified margin. It is important that sufficient historical data exist to define the effect of the control regimen with which the alternative regimen can be compared.

The ethical challenge when using an NI study design is the effectiveness of the active control. If an active control is not very effective, the experimental therapy only has to be equally effective to an ineffective option. This is particularly problematic when examining interventions for life-threatening events. For example, if a cardiovascular medication has been used in pediatric patients with 20% effectiveness, an NI study design would have to show that the experimental therapy achieves a minimum of 20% effectiveness. Most researchers and clinicians would state that 20% effectiveness is disappointingly low. It is important that researchers understand the baseline of active control before embarking on an NI study design.

First-in-Human Pediatric Clinical Trials

Certain disease states are unique to the pediatric patient population (e.g., Kawasaki disease and neuroblastoma). Therefore, experimental therapies for pediatric-specific diseases must first be introduced directly to pediatric patients rather than to adults. These first-in-human interventions are based on previous in vitro, in silica, and preclinical work in animal models. Although significant scientific work is done before use in patients, the ethical dilemma remains regarding whether the intervention offers a direct benefit to the patient. Ethicists often contend that patients are misled with first-in-human studies because it implies that the patient will receive direct benefit from the study; rather, patients should be informed that this is truly an experimental intervention and no direct benefit may be provided.

Another ethical challenge associated with pediatric first-in-human trials is the initial starting dose of the experimental agent. Dosing is often a result of pharmacokinetic modeling in addition to toxicity studies. An initial dose is designed to target the therapeutic effect while reducing the likelihood of toxicity. This becomes even more challenging in pediatric patients because doses need to be adjusted by weight or body surface area rather than a standard adult dose. Maturation rates of drug-metabolizing enzymes and drug transporters, as well as differences in the ontogeny of organs in neonates and infants, make it difficult to predict drug disposition in the pediatric population. Investigators often “err” on the conservative side of a dosing regimen in first-in-human studies to avoid adverse effects, which may lead to undertreatment and therapeutic failures. Thus, any potential benefit to the patient is unrealized in these initial studies.

CHALLENGES IN CONDUCTING PEDIATRIC RESEARCH

As we have described, conducting research in pediatric populations is inherently difficult. In addition to the common hurdles associated with general clinical research, conducting

studies in pediatric patients comes with a unique set of challenges. Issues of guardianship, researcher competencies, barriers to recruitment, the role of compensation, and commercial sponsorship all have magnified roles in pediatric research. We will briefly consider each of these hurdles in more detail.

Guardianship

Guardianship is a term used to describe someone who is either chosen or appointed to make legal decisions for another person unable to make these decisions on his or her own. Guardianship issues with children can quickly become legally complex, and guardianship can occur with or without the termination of parental rights. If parenteral rights remain in the presence of alternative guardianship, it can be unclear to the investigator who can legally make decisions regarding a child's involvement in pediatric research. One such example may arise from issues of consent. When conducting research in children for whom issues of guardianship arise, it is often difficult to ascertain issues of consent (who can consent, do both parents and guardians need to consent, etc.). For this reason, researchers often avoid approaching or enrolling pediatric patients when the guardianship is either involved or unclear. By doing so, large groups of pediatric patients often may not be well represented in pediatric clinical trials and pediatric research in general.

Adopted children as well as orphans and vulnerable children are often excluded from participating in research that may offer them substantial medical benefit because of complexities arising from guardianship. With an estimated 153 million orphans worldwide and 380,000 children in the United States living without families, a significant population of children are void of evidence-based medical interventions when they are underrepresented in clinical research because of barriers of guardianship (Kelley 2016). One common approach in pediatric research is not to allow children to enroll in studies when neither a parent nor a legal guardian is available to consent on their behalf. This approach is based on the assumption that children, by their dependent nature, are a vulnerable population. Although this approach seeks to do no harm to the patient, it may not benefit the patient in the long run. A newer approach being implemented in countries such as the United States and South Africa names the population of orphaned and vulnerable children as a special vulnerable population while allowing them to participate in clinical research using additional protective measures such as incorporating study advocates. This approach, although often costlier and more time-consuming, allows children from vulnerable populations to be represented in clinical research (Kelley 2016).

Role of Compensation

The role of compensation in medical research has been, and remains, controversial, regardless of study participant age. Opponents of participant compensation argue that

compensation reduces the voluntariness of informed consent. Proponents of compensating participants offer that it is unethical to have a patient participate in research and not be paid in some manner. It is estimated that 25% of pediatric studies currently offer some form of compensation for study participation (Caldwell 2004). Compensation for participating in pediatric trials is currently allowed in the United States; however, many countries, including those in Europe, do not allow compensation for pediatric trial participants (Caldwell 2004). Compensation issues become confounded in pediatric studies because the participants by law cannot consent to enrollment. United States federal regulations offer no guidance on compensating pediatric research participants; however, the American Academy of Pediatrics (AAP) argues that the practice of paying adolescents for participating in research is consistent with the "traditions and ethics of society." The AAP advocates for two safeguards relative to compensation in pediatric research. First, parents should receive no more than a token gesture of appreciation, and second, payments to children should not be disclosed until the study's end (Wendler 2002).

Participant compensation for medical research is quickly becoming standard practice in the United States. As it becomes more common, the issues around compensating pediatric study participants are slowly being addressed. Payments to parents must be sufficient to compensate for excess hardships incurred by study participation, such as excess costs for transportation, medical care, or food and nutrition. However, the compensation to parents or guardians must not exceed an amount that would render the payment coercive to the parents' decision to enroll the child in the clinical study.

Commercial Sponsorship

Many obstacles are responsible for the lack of pharmaceutical company involvement in pediatric studies. Costs associated with conducting trials in pediatric patients are substantially greater than costs associated with conducting similar trials in adults (Li 2007). In addition, fewer patients are often available to participate in pediatric trials, making recruitment a challenge for pediatric studies. Ultimately, the market for the end product determines whether a pharmaceutical company is willing to participate in pediatric studies because profit often drives product development. Potential return on investment in pediatric product development is often less than ideal because of smaller target patient populations for the end product relative to adult formulations. In addition, failed trials and unexpected safety issues that may arise in younger patients can quickly drive up the costs associated with conducting trials in children.

The complexity of ethical issues surrounding pediatric trials is often reason enough for pharmaceutical companies to avoid participating in pediatric trials. The dearth of investigators comfortable with participating and conducting pediatric research makes it difficult for pharmaceutical companies to

enroll enough participants to conduct trials with the power necessary to obtain statistical or even clinical relevance. Many strategies have been used in an attempt to overcome these barriers to commercial involvement in pediatric research. Formation of large pediatric clinical trial networks such as the IMPAACT (International Maternal Pediatric Adolescent AIDS Clinical Trials) Network helps ensure the availability of well-trained and qualified investigators while offering access to more pediatric patients from more geographically diverse populations. Similar pediatric clinical trial networks exist for other disease states such as oncology, cardiology, and rare or genetic-associated diseases. These networks lend a framework for pediatric studies, reducing barriers for industry involvement. A second strategy often used by commercial pharmaceutical companies is to incorporate a pediatric sub-study into a larger, predominantly adult-focused study. By doing so, investigators can ascertain the role of age as a confounding variable in treatment outcomes. In addition, with this piggyback trial design approach, operational costs can be substantially lower because existing study infrastructure is used for both the adult and pediatric portions of the study.

Research Competencies

There remains a deficit of trained clinician-investigators focused on pediatric studies. Many times, pediatric clinicians choose not to participate in clinical studies, believing that it may interrupt the patient-provider relationship. Clinicians may worry about the impressions of parents or guardians if they approach them about the possibility of enrolling their child in a pediatric trial. Other times, clinicians simply believe they lack the training and skill set to participate in clinical research. To this end, large federally funded initiatives have focused efforts on making training available in the responsible conduct of research. The NIH offers various programs directed at training clinicians to conduct pediatric clinical research. These programs consist of fellowships, training grants, continued education, and certificate programs. In addition, academic medical centers have begun to implement postgraduate training opportunities in clinical and translational research with the intent of bolstering involvement in clinical research as part of their institutional missions. Still, however, there is a deficit of clinicians and clinical staff trained and comfortable with conducting pediatric research. Often, the clinicians with training in conducting pediatric research migrate to dedicated children's hospitals with hopes of having more involvement with pediatric studies. However, this leaves a paucity of competent researchers outside these children's hospitals and academic medical centers to both enroll and fully participate in pediatric research.

CONCLUSION

Pediatric clinical research provides valuable information to clinicians, imparting to them the tools and knowledge they need to provide optimal care to their patients. With proper planning and study oversight, ethical research may be conducted in children who are often considered a vulnerable population. In this chapter, we have outlined the ethical factors affecting the successful conduct of pediatric research as well as some of the barriers to conducting research in children. We have described the regulations that govern clinical research and provided general considerations that must be made when designing and conducting research in this patient population. Although training programs for pediatric clinicians desiring to conduct clinical research have grown in number and size, a need remains for strategies to increase the number of clinicians actively involved in pediatric research.

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Self-Assessment Questions

1. In the Public Health Service syphilis study, participants were not informed that they were participating in a research study. Which one of the following ethical principles outlined in the Belmont report best describes the ethical principle most violated in the Public Health Service syphilis study?
 - A. Justice
 - B. Beneficence
 - C. Respect for persons
 - D. Clinical equipoise
2. Researchers intend to conduct a pediatric study evaluating a new broad-spectrum antibiotic for the treatment of otitis media. Because of the cost of the antibiotic, the inclusion criteria of the study include individuals who have third-party insurance because the cost of the medication will not be covered within the research protocol. Which one of the following best describes the ethical principle most violated?
 - A. Justice
 - B. Beneficence
 - C. Respect for persons
 - D. Clinical equipoise
3. A 16-year-old male adolescent who is HIV positive develops an adverse effect while taking abacavir. The medical team researches and discovers that this adverse effect has not been published in the literature. You have been asked to facilitate the publication of this case study. Which one of the following is the most appropriate next step?
 - A. Ascertain a waived consent through an institutional review board (IRB).
 - B. Obtain adolescent assent from the teenager.
 - C. Obtain adolescent assent from the teenager and informed consent from one parent.
 - D. Obtain adolescent assent from the teenager and informed consent from two parents.
4. The IRB receives a research protocol that examines the pharmacologic response to palivizumab using a new biomarker that has been validated by the company and several clinical trials. Throughout the discussion, a pulmonologist raises concerns that the investigator should be using an older biomarker for the study instead of the new one. Except for the pulmonologist's objection, the protocol is appropriate. Which one of the following is the most appropriate action?
 - A. Deny the IRB application until changes in the biomarker are made in study protocol.
 - B. Deny the IRB application because the research subjects are at risk of harm.
 - C. Approve the IRB application because the research subjects are not at risk of harm.
 - D. Approve the IRB application because the new biomarker is a better predictor of response than the older biomarker.
5. A novel fifth-generation cephalosporin receives FDA label approval. The agent covers vancomycin-resistant *Enterococcus* (VRE) spp. in addition to gram-negative organisms and anaerobes. A collaboration of researchers intends to submit an NIH research grant protocol to examine its use in the ICU. The study excludes pediatric patients because the researchers prefer not to worry about assent issues. Which one of the following is the NIH most likely to do?
 - A. Fund the study as currently written because understanding the pharmacokinetics (PK) in the adult ICU setting is important.
 - B. Fund the study as currently written because it addresses a serious health care concern related to VRE.
 - C. Not fund the study because sufficient data should have been obtained during the FDA approval process.
 - D. Not fund the study because there is no scientific explanation for why children are excluded from the study.

Questions 6 and 7 pertain to the following case.

The P-KIST study is planned for children younger than 10 years to assess the pharmacokinetic profile of a single dose of a new intravenous antihistamine. Children in the study will receive intravenous maintenance fluids, followed by the injection of the intravenous antihistamine into the running intravenous line. Serial blood sampling will take place every 2 hours for 8 hours, followed by discontinuation of the intravenous maintenance fluids.

6. Which one of the following is the best classification for the P-KIST study?
 - A. Research involving no greater than minimal risk and the prospect of direct patient benefit.
 - B. Research involving greater than minimal risk but the prospect of direct patient benefit.
 - C. Research involving greater than minimal risk but no prospect of direct patient benefit.
 - D. Eligible for waived consent.

7. Which one of the following best depicts who is ultimately responsible for assessing the appropriate level of risk in the P-KIST study?
- A. Institutional IRB
 - B. Principal investigator
 - C. NIH
 - D. FDA

Questions 8–10 pertain to the following case.

G.G. is a neonatal intensive care specialist who wishes to evaluate a practice change for term infants who are born to group B *Streptococcus*-positive mothers. Current standard of practice is to administer intravenous ampicillin for 10 days to ensure that exposed infants born vaginally do not develop late-onset group B *Streptococcus* sepsis. The medical team wishes to administer the first 3 days of ampicillin therapy intravenously, followed by 7 days of oral therapy. Blood samples will be obtained during intravenous and oral therapy to ensure that ampicillin serum concentrations are equivalent.

8. Which one of the following best describes the appropriate risk level for G.G.'s study?
- A. No risk category; this is a standard of practice, albeit in a different dosing form.
 - B. Research involving no greater than minimal risk.
 - C. Research involving greater than minimal risk but direct benefit to patient.
 - D. Research involving greater than minimal risk but no direct benefit to patient.
9. G.G.'s research protocol is initiated, and subject recruitment is going well. The team would like to enroll an infant in the study, but the mother is sole guardian, and she is currently in the adult ICU. The infant's grandmother offers to sign the informed consent because she wants the child to be home while the mother is recovering in the hospital. Which one of the following is the best course of action regarding G.G.'s study?
- A. Allow the grandmother to sign the informed consent as a surrogate for the incapacitated mother.
 - B. Exclude the infant from study participation.
 - C. Continue with the plan to change the infant from intravenous to oral ampicillin, as planned, without informed consent.
 - D. Enroll the infant now and obtain informed consent from the mother when she is medically able to do so.
10. G.G.'s research team is notified that the mother has rapidly improved and is now able and willing to discuss the study protocol. However, English is her second language, and she has difficulty communicating with the research

team. Which one of the following is the best action for the research team to take?

- A. Provide adequate information (written and verbally) about the study in a language understandable to the participant.
- B. Note in her medical chart that she provides verbal informed consent.
- C. Exclude the infant from the study because the informed consent sheet is not available in the mother's native language.
- D. Continue to transition the infant from intravenous to oral therapy.

Questions 11–14 pertain to the following case.

The DOPPTOP research team wishes to examine the relationship between traumatic brain injury (concussions) and cerebral blood flow. Cerebral blood flow will be measured using an innovative Doppler ultrasound "helmet" that measures blood flow velocity. Those with concussions will be matched with controls to examine potential differences in blood flow between the two groups. To obtain the best results and avoid the co-variable of anxiety affecting cerebral blood flow, all patients enrolled in DOPPTOP will receive a small dose of oral midazolam before measurements are taken.

11. Which one of the following is the most appropriate risk category for DOPPTOP?
- A. Research involving no greater than minimal risk
 - B. Research involving greater than minimal risk but the prospect of direct benefit to patient
 - C. Research involving greater than minimal risk but no prospect of direct benefit to patient
 - D. Not eligible for waived consent
12. The DOPPTOP study is approved by the institutional IRB. A 14-year-old girl volunteers to serve as the control in the study, and the appropriate informed consent is obtained. In reviewing the adolescent assent form, the researcher becomes concerned that the teenager does not understand the risks associated with the study. Which one of the following would be the most appropriate next step for the DOPPTOP research team?
- A. Do not enroll the patient because she does not understand the risk associated with the study.
 - B. Use the youth assent form because it may more clearly convey the risks associated with the study to the patient.
 - C. Document in the chart that the patient understands the scope of the research protocol, even though she cannot understand the adolescent assent form.
 - D. Encourage the patient to sign the adolescent assent form because she understands the risks sufficiently.

13. While conducting DOPPTOP, a 16-year-old male adolescent with a history of concussions agrees to participate in the study. The appropriate assent and consent forms are filled out, and later the teenager attends the outpatient clinic to have the cerebral ultrasound. After consuming the oral midazolam at the outpatient clinic, the research subject objects to participating in the study. His mother states that “it is just the medicine talking” and urges the researchers to proceed. Which one of the following is the best course of action for the DOPPTOPP research team?
 - A. Proceed with the study because the mother, who signed the informed consent sheet, said it was appropriate to proceed.
 - B. Discontinue to study because the teenager revoked assent.
 - C. Discontinue the study because the mother said it was appropriate to do so.
 - D. Wait several hours until the drug effects wear off and ask him to participate again without re-obtaining assent.
14. A parent wishes to enroll his child to serve as a control in the DOPPTOPP study. As the research team discusses the protocol with the parent, it becomes apparent that the parent is most interested in the \$200 gift card that is provided as compensation for the child participating in the study. Which one of the following best describes the ethical principle most compromised in this situation?
 - A. Justice
 - B. Beneficence
 - C. Respect for persons
 - D. Clinical equipoise
15. An infectious disease physician wants to study two-drug therapy for HIV infection in treatment-naïve adolescents for whom the current standard of care is triple-drug therapy. The physician believes the added risk of adverse effects from three drugs does not outweigh the efficacy benefit of the third drug. Which one of the following study designs would best answer this question?
 - A. A randomized controlled trial in which the control arm is placebo and the active arm is two-drug therapy.
 - B. A non-inferiority trial in which two-drug therapy is studied against three-drug therapy for HIV.
 - C. A cohort study of patients receiving two-drug therapy comparing efficacy with historical control data of three-drug therapy.
 - D. A non-inferiority trial of two separate regimens consisting of two drugs active against HIV.
16. Which one of the following best describes pharmaceutical companies’ involvement in pediatric clinical trials?
 - A. Pharmaceutical companies eagerly participate in studies focused on pediatric drug development because the return on investment is often greater than in adult clinical trials.
 - B. Pharmaceutical companies are mandated by federal law to enroll equal numbers of adults and adolescents in any trial expected to garner FDA approval.
 - C. The barriers to pharmaceutical company involvement in pediatric clinical trials are greater for pediatric trials than for adult trials and thus often discourage industry involvement in the pediatric trials.
 - D. Pharmaceutical company involvement in pediatric clinical trials is strong because recruiting patients is easier than in an adult trial, and there are more trained investigators for pediatric research than for adult studies.
17. A 6-year-old girl, an orphan, lives in a suburban group home in southern California. She has a rare genetic disease that would make her eligible for a clinical trial at a nearby children’s hospital. Which one of the following would be the biggest concern regarding this child’s involvement in the study?
 - A. She would not be considered for enrollment because she is an orphan, and her biological parents would be unable to consent to the study.
 - B. She can enroll in the study as long as she meets the inclusion and exclusion criteria for the study; she must provide consent before enrolling because she has no parents to assent for her.
 - C. She can enroll in the study if she meets the inclusion and exclusion criteria but must provide assent; the assent form used for the study should be written at a level she can understand. No further consent is needed.
 - D. For her to enroll into the study, a legal guardian would need to provide consent.
18. Which one of the following best describes the training requirements of investigators involved in pediatric clinical trials?
 - A. Pediatric trials are managed similarly to adult trials; thus, the investigators need no special training.
 - B. Investigators involved in pediatric clinical trials are required to have a special certification from an academic medical center justifying their competency in conducting pediatric research.
 - C. Pediatric clinicians are often hesitant to participate in pediatric clinical trials because they often

believe they lack the training needed to manage the complex issues that arise from enrolling pediatric patients.

- D. Physicians for adult patient populations are often used to carry out pediatric clinical trials because there is a lack of trained pediatricians to participate in pediatric trials.
19. A 12-year-old boy recently received a diagnosis of neuroblastoma. The pediatric oncologist managing the boy's care would like to enroll him in a study in which biopsied tissue from the tumor will be studied by a local pathology laboratory to determine the genetic characteristics underpinning the tumor's characteristics. Results from the study will not affect the immediate care of the patient. Which one of the following best describes the child's enrollment in the study?
- A. The study will not need IRB approval because no intervention is occurring for the patient; he is simply providing a tissue sample to the investigator.
- B. The study will need IRB approval; the patient will need to provide assent, and his parents will need to provide consent for him to participate.
- C. The oncologist managing the boy's care will be responsible for signing the consent form for his involvement in the study because the oncologist is the most knowledgeable provider regarding study procedures.
- D. Neither the boy nor his parents should receive any type of compensation for participating in the study because the tumor biopsy would have occurred at some point in his care anyway.
20. Which one of the following best describes the conduct of first-in-human trials in pediatric populations?
- A. They may never be conducted in pediatric populations. Adult clinical trial data must first be available so that investigators can scale dosing appropriately for children.
- B. Dosing in these trials may be based on preclinical studies.
- C. They are unethical to conduct in pediatric populations.
- D. To conduct first in human trials in children, the dose selected for the study must be proven to provide efficacy for the pathophysiologic state being studied.

Learner Chapter Evaluation: Ethical Considerations in Pediatric Research.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

1. The content of the chapter met my educational needs.
2. The content of the chapter satisfied my expectations.
3. The author presented the chapter content effectively.
4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
5. The content of the chapter was objective and balanced.
6. The content of the chapter is free of bias, promotion, and advertisement of commercial products.
7. The content of the chapter was useful to me.
8. The teaching and learning methods used in the chapter were effective.
9. The active learning methods used in the chapter were effective.
10. The learning assessment activities used in the chapter were effective.
11. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

12. Apply the ethical principles described in the Belmont Report.
13. Demonstrate the concepts of beneficence, justice, and respect for persons as they relate to pediatric research.
14. Discover study design issues that are implicated by the inclusion of pediatric subjects.
15. Evaluate challenges to conducting research in pediatric populations.
16. Please provide any specific comments related to any perceptions of bias, promotion, or advertisement of commercial products.
17. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

Study Design in Pediatrics

By Mary Jayne Kennedy, Pharm.D., DABCP

Reviewed by Mary Ryan, Pharm.D., BCPPS; and Melissa Ray, Pharm.D., BCPS, BCPPS

LEARNING OBJECTIVES

1. Justify when a pediatric study is scientifically necessary and when extrapolation from adult data is valid.
2. Evaluate design issues unique to pediatric drug studies for each age category (neonates, infants, children, and adolescents).
3. Design a clinical study for a child of any age.
4. Apply the principles of developmental pharmacology in the design, conduct, and interpretation of pediatric studies.
5. Develop and apply strategies for overcoming the challenges of conducting clinical trials in children.
6. Judge whether a research protocol is appropriate for conduct in a child of a given age.

ABBREVIATIONS IN THIS CHAPTER

IRB	Institutional review board
PBPK	Physiologically based pharmacokinetic modeling

[*Table of other common abbreviations.*](#)

INTRODUCTION

Children are large consumers of medications, with over 200 million outpatient pediatric prescriptions dispensed annually in the United States (Chai 2012). About one in five children and one in three adolescents take a prescription medication for a chronic condition, and almost 7% of children regularly take two or more prescription drugs (Gu 2010). Given the increasing frequency of “adult” diseases in the pediatric population requiring pharmacologic therapy (e.g., type 2 diabetes, hypertension, hypercholesterolemia) and the expanding use of drugs for conditions traditionally managed nonpharmacologically (e.g., sleep disorders, behavioral disorders), medication use in children will only continue to rise. It is estimated that the global market for pediatric medications will reach over \$100 billion by 2019 (BCC Research 2014). Information regarding the safety and efficacy of medications in children is greatly needed to guide rational pharmacotherapy decisions.

With respect to drug prescribing, children were historically considered small adults, and therapeutic decisions were based solely on differences in weight or size. Children were also largely excluded from clinical trials because of ethical concerns and lack of infrastructure and expertise to conduct such studies. Consequently, children were considered “therapeutic orphans,” and off-label prescribing was the rule rather than the exception. Given age-specific differences in the underlying processes responsible for drug action and the dose-exposure-response relationship, it is now apparent that this strategy is inadequate and potentially harmful, as evidenced by the many medication-related therapeutic tragedies in children (e.g., chloramphenicol and gray baby syndrome, benzyl alcohol and neonatal gasping syndrome).

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- Principles of developmental pharmacology
- Statistical analysis and sample size estimation
- Basic pharmacokinetics and pharmacodynamics
- Fundamentals of pediatric therapeutics and pharmacotherapy

[Table of common pediatric laboratory reference values.](#)

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- FDA. [Research in Children](#) [homepage on the Internet].
- National Institutes of Health. [Making Medicines Safer for Children: NICHD-Supported Research in Pediatric Pharmacology of Child Health and Human Development](#) [homepage on the Internet].

Legislative initiatives over the past 2 decades, including the FDA Modernization Act (1997), the Best Pharmaceuticals for Children Act (2002), the Pediatric Research Equity Act (PREA 2003), the FDA Amendments Act (2007), and the FDA Safety and Innovation Act (2012), have led to a dramatic increase in the number of studies conducted in children. As of 2015, there have been over 500 pediatric labeling changes, which include information about pediatric dosing, safety, and/or efficacy (Addy 2015).

Off-label use remains an important public health issue for infants, children, and adolescents, however, because many drugs still do not include information regarding pediatric use. Despite the legislative requirements for pediatric data, it still takes an average of 8 years from the time the drug is approved in adults for pediatric information to include in the drug label (Mehrota 2016). During this lag time, the drug is used off-label. Furthermore, almost 50% of pediatric studies submitted for review to the FDA in 2007–2014 failed to establish safety and/or efficacy because of critical study design flaws (e.g., poorly defined end points, inadequate sample sizes), leading to the FDA's inability to approve the revised product labeling for pediatric use (Wharton 2014). It is therefore critical that pediatric studies be designed with an understanding of the unique nature and challenges of conducting research in children across the age spectrum in order to provide rigorous and scientifically valid data that can support the successful integration and application of information into clinical practice.

WHEN IS A PEDIATRIC STUDY NECESSARY?

Several factors must be considered when determining whether a pediatric study is necessary. These include the prevalence of the condition to be treated in the pediatric population, the seriousness of the condition to be treated, the availability and suitability of alternative treatments for the condition, the need for development of pediatric-specific end points, and the age ranges of children likely to be treated (ICH 2000). The presence of a serious or life-threatening disease for which a drug represents a potentially important advance in therapy is perhaps the most compelling indication for conducting a pediatric trial. Similarly, developing drugs for diseases exclusively affecting children necessitates the conduct of pediatric trials. Even when there is an adult disease correlate, pediatric-specific studies should be considered unless use of a specific product in the pediatric population is clearly inappropriate.

Scientific Necessity vs. Extrapolation

Children are widely considered a vulnerable population that, as research participants, requires additional protections beyond those afforded to competent adults [US 21 CFR 56.111(a)(1) and (b)]. The need to conduct studies in children must therefore be carefully balanced with the responsibility to protect them from the potential risks of participating in a clinical trial. Scientific necessity, a fundamental ethical principle of pediatric research, is the primary consideration in determining whether a study should be conducted in children. This principle is founded on the premise that children should not be enrolled in a clinical investigation unless necessary to achieve an important scientific and/or public health objective concerning the health and welfare of children (Roth-Cline 2015). Children should also not be enrolled in studies that are duplicative or are unlikely to yield important knowledge applicable to children about the product or condition under investigation.

The ethical principle of scientific necessity has been operationalized in the scientific principle of extrapolation. As generally understood, extrapolation is defined as the process of using known information or facts to make inferences or conclusions about the unknown. In clinical trials, extrapolation refers to using data from another population to make inferences about or predict outcomes in a different population. The concept of extrapolation in pediatric clinical pharmacology studies was first introduced in the Pediatric Labeling Rule (1994) as a means to minimize the number of subjects needed to enroll in pediatric clinical trials while maximizing the usefulness of the data obtained and preserving scientific rigor. The PREA subsequently outlined specific conditions under which extrapolations of efficacy or effectiveness in children could be made using existing data in adults. Specifically, PREA states that “if the course of disease and the effects of the drug are sufficiently similar in adults and pediatric patients, the Secretary [FDA] may conclude that

pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies” (21 CFR 355c). This constitutes the legal definition of extrapolation of drug efficacy or effectiveness in the United States.

FDA Guidance and Algorithms

The FDA has developed a Pediatric Study Planning & Extrapolation algorithm for determining the need for pediatric studies using the principles of scientific necessity and extrapolation (Figure 2-1). This algorithm is included in the Draft Guidance for Industry titled General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological

Products (DHHS 2014). The European Medicines Agency and the International Council for Harmonisation set forth similar frameworks to guide pediatric drug development both in the European Union (EU) and worldwide (EMA 2016; ICH 2000). Under the FDA algorithm, the three possible approaches to a pediatric study differ with respect to the extent of extrapolation that is acceptable (full, partial, or none). These approaches are based on (1) the similarities between children and adults with respect to disease progression, response to intervention, and the exposure-response relationship; (2) the ability to measure the drug and/or active metabolites and to use these concentrations to predict clinical response; and (3) the availability of pharmacodynamic (PD) measurements that can be used to predict efficacy in children.

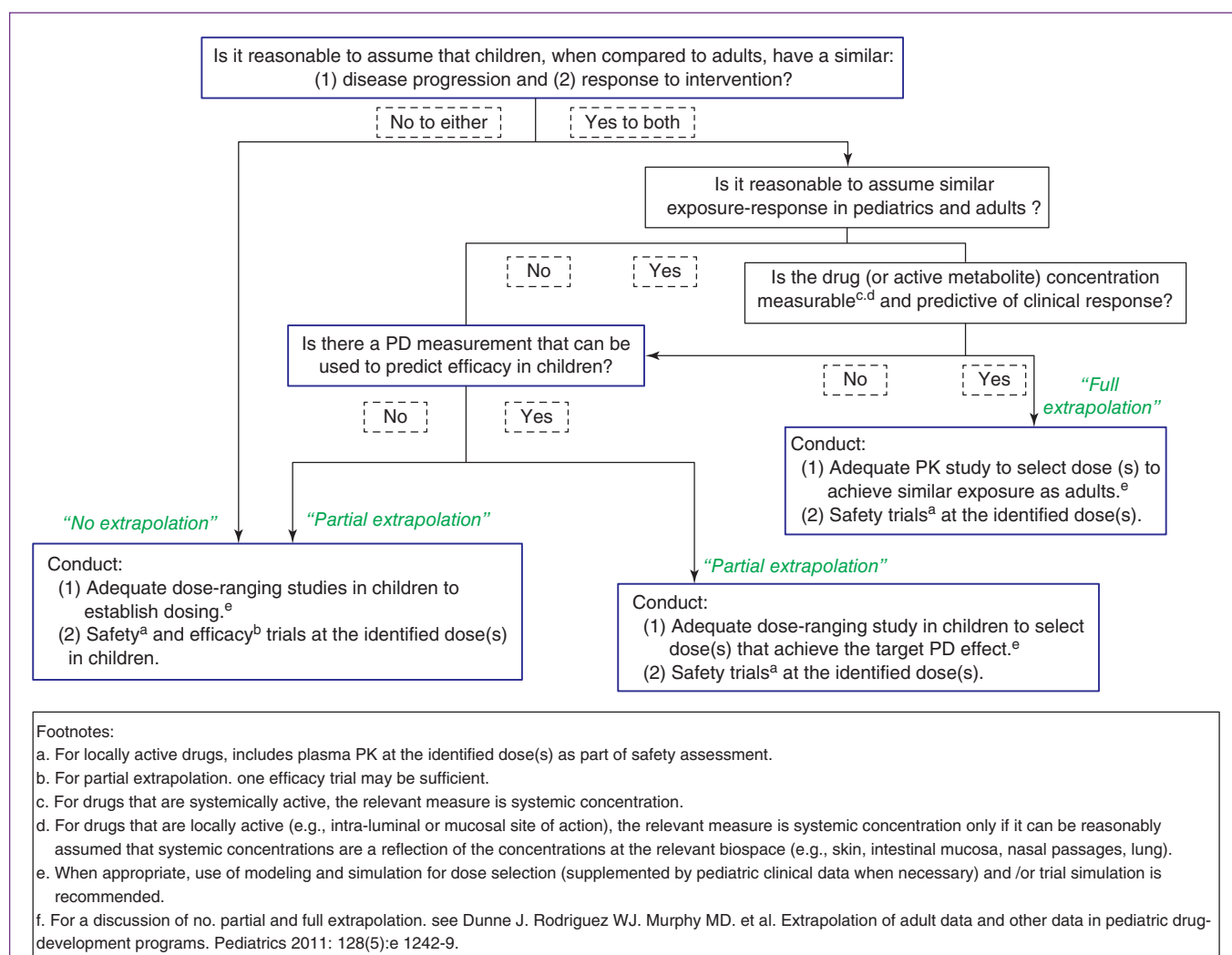


Figure 2-1. FDA pediatric study planning and extrapolation algorithm.

Reprinted from: U.S. Department of Health and Human Services (US DHHS). Food and Drug Administration. Center for Drug Evaluation and Research. General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products. Draft Guidance. December 2014.

The pharmacokinetic (PK)-only approach (full extrapolation) assumes that “compared to adults, children have (1) a similar progression of disease; (2) a similar response of the disease to treatment; (3) a similar exposure-response or concentration-response relationship; and (4) the drug (or active metabolite) concentration is measurable and predictive of the clinical response” (DHHS 2014). Evidence that could support a conclusion of similar disease course and similar drug effect in adult and pediatric populations includes “evidence of common pathophysiology and natural history of the disease in the adult and pediatric populations, evidence of common drug metabolism and similar concentration-response relationships in each population, and experience with the drug or other drugs in its therapeutic class in the disease or condition or related diseases or conditions” (DHHS 2014). If there is no currently used pediatric dose, if PK information about a currently used pediatric dose is insufficient, or if the currently used pediatric dose in the same clinical context would not be expected to match adult exposure, a PK study should be conducted to identify the pediatric dose that will provide similar exposure in adults (DHHS 2014).

The PK and PD approach (partial extrapolation) is applicable when the disease and intervention are believed to behave similarly in pediatric patients and adults but the exposure-response relationship in pediatric patients is either inadequately defined or thought not to be sufficiently similar (DHHS 2014). The level of pediatric evidence required to support partial extrapolation is based on whether PD measurements that can be used to predict efficacy in children are available. If the answer to this question is yes, efficacy trials are not required. However, a dose-ranging study should be conducted to select the dose that achieves the target PD effect, which should be followed by safety studies at the identified target dose. Conversely, if there are no PD measurements to predict pediatric efficacy, efficacy trials must also be conducted together with safety studies at the dose identified in the dose-ranging study. The PK and efficacy approach (no extrapolation) should be used “if the disease progression is unique to pediatrics or its progression and/or response to intervention is undefined or dissimilar to that in

adults” (DHHS 2014). In this situation, “substantial evidence of the effectiveness and safety of the drug in pediatric subjects in one or more clinical studies is required” and usually evaluates more than one dose (DHHS 2014).

Extrapolation of efficacy has been used extensively in pediatric drug development programs and in studies submitted in response to FDA-issued written requests to support pediatric drug labeling (Dunne 2011). Between February 1998 and February 2009, 370 pediatric studies were submitted to the FDA for 166 products, and extrapolation of efficacy data (from adults or other pediatric age groups) was used to support approval for 82.5% of the products. When extrapolation was used, 61% of the drug products obtained a new pediatric indication or extension into a new age group, which decreased to 34% when there was no extrapolation. Analyses of these data clearly show that extrapolation can be used successfully to support drug approval for pediatric use. They also highlight an important issue, however, with respect to the strength of evidence required to show the degree of similarity between adult and pediatric populations and the potential implications of incorrect assumptions. Other than conducting the trial in the intended population of use, there is no way to guarantee that a given drug will elicit the desired response without adverse consequences, and it is impossible to determine with absolute certainty whether the evidence used to support the decision to extrapolate truly reflects how the agent will act when given to a given patient. Consequently, if the assumptions underlying extrapolation are untrue, there is the risk of labeling drugs as effective when they are, in fact, ineffective. The decision to extrapolate must therefore be weighed carefully against the potential implications of mislabeling a drug for pediatric use.

Age and Regulatory Guidance

Age ranges and definitions for pediatric trials are usually defined using current regulatory guidance documents, which divide the pediatric population into cohorts using certain breakpoints (Table 2-1).

Although somewhat arbitrary, these breakpoints are intended to group children according to known developmental

Table 2-1. Comparison of Pediatric Age Definitions		
	Center for Drug Evaluation and Research (CDER)	International Council for Harmonisation (ICH)
Neonates or newborns	Birth to 1 month	0–27 days
Infants and toddlers	1 month – 2 years	28 days – 23 months
Children	2–11 years	2–11 years
Adolescents	12–16 years	12–18 years

Information from: FDA. Center for Drug Evaluation and Research. General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products. Draft Guidance. December 2014; and International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartate Guideline. Clinical Investigation of Medicinal Products in the Pediatric Population E11. December 2000.

changes in pharmacology and biology that influence the dose-exposure-response relationship. However, the proposed age categories may include different maturation levels or considerable developmental overlap. Adopting a flexible approach to age designation is therefore required to ensure that study design reflects current knowledge of pediatric pharmacology and developmental biology (DHHS 2014; ICH 2000).

COMMON TYPES OF PEDIATRIC PHARMACOLOGY STUDIES

Because of legislative initiatives over the past 2 decades, the number of pediatric studies has increased dramatically, and the types of studies conducted have largely been driven by legislative requirements. Consequently, the most common types of pediatric pharmacology studies are those that support new or expanded labeling of drugs for use in children (PK, PD, safety, and efficacy). As a provision of the 2007 FDA Amendments Act, sponsors planning to submit a marketing application for a drug that includes a new active ingredient, indication, dosage form, dosing regimen, or route of administration are required to submit an initial pediatric study plan outlining the types of pediatric studies that are planned. An initial pediatric study plan should also be submitted for drugs that are being developed specifically for use in pediatric populations. The FDA published a draft guidance document for developing an initial pediatric study plan, with an updated version of this guidance released in March 2016 (DHHS 2016). The International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use has developed a similar guidance (ICH 2000).

PK and PD Studies

Pharmacokinetic studies are one of the two types of studies required under all three extrapolation approaches outlined by the FDA (full, partial, or none) and are used to determine the level and extent of drug exposure in the pediatric population. Pharmacokinetic studies are also used to determine the dose that will produce the target exposure level. In most cases, PK studies are conducted in children who have the disease of interest rather than in healthy volunteers, which increases intersubject variability but more accurately reflects clinical use. Because the processes of growth and development can affect the underlying processes governing drug absorption, distribution, metabolism, and elimination, PK studies conducted in each pediatric age group may be necessary.

When used together with safety studies, PK studies across the age range of pediatric patients likely to receive the medication may provide sufficient information by facilitating a selection of pediatric doses that will produce blood concentrations similar to those in adults (full extrapolation). However, an approach based on PK is likely to be insufficient for drugs whose blood concentrations do not correlate with

efficacy or when there is a concern that the concentration-response relationship may differ between children and adults (partial extrapolation). Therefore, PD studies should also be conducted, whenever possible, to characterize the exposure-response relationship. These studies can include an assessment of the effect of the drug on biomarkers or clinical end points for both effectiveness and safety and may afford a better understanding of whether the PK-PD relationship of the drug in children is similar to that observed in adults (DHHS 2014). When a clinical end point cannot be measured directly, an appropriate biomarker should be selected to substitute for the desired end point according to experience in adults.

Efficacy and Safety

To be labeled for use in children, evidence must be adequate that the drug is both safe and effective in the intended age group. Evidence of efficacy can be provided by conducting pediatric-specific studies or extrapolating from adults or another pediatric age group. Extrapolation of efficacy is based on the core assumption that the mechanistic pathways of the disease being treated and the mechanisms of action of the drug used to treat the disease are similar in both adult and pediatric patients. If this core assumption is not met, the effectiveness of the drug product must be shown in one or more pediatric clinical studies usually evaluating more than one dose (DHHS 2014).

Safety studies, in contrast, are required for all drugs being evaluated in children and must be conducted together with PK and PD studies (when required). This is because the type, frequency, and/or severity of a given adverse effect can differ dramatically in adults and children, limiting the ability to extrapolate safety data. Drugs may also affect physical and cognitive growth and development, and the impact of drugs on these processes may not be apparent until much later. Long-term studies or surveillance data may therefore be needed to determine possible effects on skeletal, behavioral, cognitive, sexual, and immune maturation and development.

Formulation

Developing age-specific formulations that facilitate accurate dosing and patient adherence (e.g., liquids, suspensions, and chewable tablets) is an important part of the evaluation process for medications in the pediatric population during both the pre- and postmarketing phases. The FDA requires that formulations be addressed in the initial pediatric study plan and that studies be conducted as necessary. Depending on the active substance and excipients, a new formulation may be required, or information about dilution of an existing formulation must be generated.

Given that the toxicity of some excipients may vary across pediatric age groups and between adult and pediatric populations (e.g., benzyl alcohol and newborns), use of excipients such as alcohol, polymers, preservatives, and plasticizers should also be carefully evaluated. Taste and texture are also

important considerations in children. For injectable drugs, developing needle-free delivery devices and other noninvasive alternatives such as transdermal patches and inhalable formulations is also a priority.

GENERAL CONSIDERATIONS IN PEDIATRIC STUDY DESIGN

Pediatric studies present unique design and implementation challenges that require careful planning and consideration before initiating a study (Box 2-1).

The implications of conducting improperly designed studies of children are significant and can lead to trial failure. Study design was identified as a potential contributing factor in 30% of drug trials submitted to the FDA in 2007–2014 that failed to establish a new or expanded pediatric indication (Momper 2015). Examples of issues identified include inappropriate dose selection, lack of a control group, lack of a well-designed and executed efficacy study, assay sensitivity, choice of the clinical margin in a noninferiority trial, and postrandomization exclusion of placebo responders. These examples highlight the need to select clinical trial designs that are interpretable and that provide a meaningful and generalizable trial outcome.

Population Selection

When identifying a target study population, the intended use of the drug in the pediatric population should be considered. In most cases, this is driven by the approved adult indication. In general, pediatric pharmacology studies should be conducted in children who are receiving therapy for a particular indication, and most regulatory guidelines require that the study be conducted in patients who have a condition for which the drug could be used for treatment (DHHS 2014; ICH 2000). In rare instances, however, studies may also be conducted in children at risk of a given condition of interest. Age-related differences in disease prevalence that can affect the balance of subjects across a cohort must also be considered (Abdel-Rahman 2007). For example, a study designed to characterize the influence of age on the disposition of an oral antihypertensive agent may be difficult to conduct, given that essential hypertension rarely exists before adolescence and the incidence of secondary hypertension without significant comorbidity

is extremely low. A study developed with disease-designed exclusion criteria that includes an inappropriate (i.e., unaffected) age group will be slow to enroll and may terminate without accruing an adequate number of patients.

Given that most studies are conducted to define the age-appropriate doses necessary to produce a level of systemic exposure comparable with that in adults, age is often the primary driver of the constitution of a study cohort. Selection of the study cohort cannot be based solely on age, however, and many other factors may need to be included in the process (Abdel-Rahman 2007). Children are a highly dynamic population and can change during a single study, complicating design and data interpretation. Consequently, the expected intra- and intersubject variability that may be produced by the process of normal growth and development should be incorporated into the initial trial design. The collective impact of development, disease, environment, and genetics should also be considered.

Chronologic vs. Developmental Age

Although an age-driven strategy for patient selection may yield information that characterizes the effect of development on drug disposition, in some instances, age-based categorizations fail to consider that physiologic development occurs along a continuum. Consequently, there may be many discrete subpopulations within each age-stratified patient cohort. The concept of developmental age, introduced in 1994 as part of the “Pharmacokinetics and Pharmacodynamics in Adolescents” joint workshop, encompasses the idea that developmental changes in drug PK and PD occurring as the result of pubertal development (i.e., Tanner stages) may be better understood within the context of the underlying mechanisms responsible for their occurrence (Finkelstein 1994). It also purports that, for processes that change with development, use of chronologic age as a surrogate or indicator may be very misleading. For example, in children of the same chronologic age, the hormonal milieu may be substantially different, depending on the stage of pubertal development. For processes affected by hormonal fluctuations such as drug-metabolizing enzyme activity, a biomarker that more accurately reflects the underlying hormonal changes should be used.

Sample Size Considerations

Many pediatric clinical trials lack a sufficient number of patients to fully assess safety, including adverse events. This is largely because of the many challenges associated with identifying, recruiting, and enrolling children in clinical trials. In the United States, children make up about 23% of the population, and only a few children have a specific given disease (U.S. Census Bureau 2016). Consequently, there is a relatively small population base for any given disease. This is further complicated by the need to enroll a given number of children with a specific disease in each of the different

Box 2-1. Design and Implementation Challenges in Pediatric Studies

- Selecting the target study population
- Determining the most appropriate dosing approach
- Identifying an age-appropriate formulation and administering the study drug
- Identifying measurable and meaningful outcomes and end points
- Measuring drug concentrations and determining the most appropriate sampling scheme

trial arm age cohorts. Considering the constraints on subject enrollment, many trials must recruit internationally to enroll a sufficient number of patients, which significantly increases the time needed to successfully complete a given study. Generalizability of data from international trials is a concern; therefore, caution must be taken to evaluate potential covariates such as ethnicity, diet, genetics, and environment that might influence results from multinational trials.

The need to obtain adequate subject numbers must be carefully balanced with the risk of overuse of the same children in several clinical trials, a situation that commonly occurs in some populations such as in children with cancer or cystic fibrosis. Justification for the sample size must also be provided and should include parameters such as the effect size/minimum detectable difference, estimated population variability, power, and confidence interval, when relevant. Recommendations regarding the sample size required for pediatric PK studies have been published by the FDA, stating that studies must be “prospectively powered to target a 95% confidence interval within 60% and 140% of the geometric mean estimates of clearance and volume of distribution in each pediatric sub-group with at least 80% power” (Wang 2012).

Dosing Approach

Identifying the correct dose for use in pediatric trials is critical, particularly when the drug is being studied for a disease that has a different underlying etiology and/or pathophysiology in children from that in adults. When selecting initial doses for children, it is essential that the principles of developmental pharmacology and physiology be considered together with known PK and PD information in adults and/or other pediatric age groups (if available). The pharmacologic characteristics of the drug and the safety/toxicity profile must also be considered. Pediatric dose calculations have traditionally been based on the principles of allometric scaling, in which a fraction of the adult dose is administered. Normalization of doses for weight or size and fixed dosing across the continuum of subject ages are also commonly used strategies. More recently, modeling and simulation techniques such as physiologically based PK (PBPK) are useful tools to inform the selection of initial pediatric doses, given that they incorporate known drug-dependent (e.g., clearance, metabolism) and system-dependent (e.g., protein binding, enzyme and transporter activity) parameters from studies of adults and other pediatric cohorts. Regardless of the strategy used, a range of doses should be evaluated, whenever possible, to determine whether a level of drug exposure beyond what is efficacious in adults is necessary. This is particularly important when treating a pediatric disease that is clinically distinct from a similar disease in adults.

Target Exposure Levels and Exposure-Response Relationship

When existing data suggest that the exposure-response relationships in adults and children are similar, dose selection is

driven by the goal of achieving a level of systemic drug exposure shown to be safe and efficacious in adults. In many cases, this is accomplished using study designs that incorporate weight- or body surface area–normalized dosing such that exposure estimates are comparable across the cohort of children being evaluated. Intersubject PK variability, which is substantially higher in children than in adults and has been identified as a potential contributor to trial failure, must also be considered (Momper 2015). When matching drug exposure in children to that in adults, studying several doses across the tolerated dose range is the most reasonable approach to avoid study failure as the result of incorrect dose selection. However, given limitations on subject recruitment and enrollment, studying several doses may not always be practical or feasible. If the exposure-response relationship in adults and children is different, this should be accounted for in the range of doses selected. For example, children are known to be less sensitive to antihypertensive drugs than adults. In pediatric antihypertensive studies, it is therefore reasonable to select doses that will provide a greater level of exposure than that observed with the labeled adult dose, provided this approach is justified by prior safety and exposure-response studies of adults (DHHS 2014; Benjamin 2008).

Weight Normalization

Normalization of doses to body mass (milligram per kilogram) or surface area (milligram per square meter) is a commonly used strategy for initial dose determination in pediatric studies. With this strategy, each child receives a comparable weight-adjusted dose. This approach can give a good estimate of the required pediatric dose in populations when there are no ongoing, dynamic changes in the underlying processes determining drug absorption, distribution, metabolism, and elimination (e.g., adolescents). Administering the same weight-normalized dose to all subjects also eliminates the need for dose normalization of exposure in data analysis. If the formulation does not allow for dose titration, however, normalization may not always be feasible or practical (Abdel-Rahman 2007). Normalization also does not consider the impact of ontogeny on drug metabolism, clearance, and transport; therefore, the physiologic development of the intended population must be considered.

Fixed Dosing

Fixed dosing, in which a standard dose (in milligrams) is administered across the continuum of subject ages and body weights, is another approach to dose selection used in pediatric studies (Abdel-Rahman 2007). This approach provides a dynamic range of milligram/kilogram doses and is commonly used when no formulation is available that can be easily titrated. It also may be the dosing strategy of choice when the goal is to evaluate a range of doses. Fixed dosing can be used in lieu of a dose escalation approach to provide a more complete evaluation of dose proportionality than

might be afforded in studies in which only two or three normalized doses are evaluated (Abdel-Rahman 2007). However, this approach assumes that absorption is linear across the range of doses and requires that exposure estimates be dose normalized when evaluating the influence of age on drug disposition.

Use of Placebo

Use of placebo controls in pediatric clinical trials remains controversial. Under federal regulations, institutional review board (IRB) approval may be granted for research in children involving a placebo control group if at least one of the following two criteria are met: (1) the balance of potential harms and benefits for subjects in the placebo arm must be as favorable as for those receiving the active treatment and (2) the potential harms in the placebo arm are no more than minimal or involve only a minor increase over minimal risk. In general, placebo-controlled studies of children are acceptable to establish a baseline comparison if there are no approved standard-of-care or adequately studied treatments for the disease under investigation. Exposure to placebo should be minimized, however, with respect to the number of subjects needed, the randomization ratio, and the study duration. The study protocol should also include a plan for early withdrawal of the placebo in a randomized design or incorporate the planned use of rescue medication in order to ensure that all subjects are given access to the potential benefits of the study drug. Given that parents are more likely to consent to participation in a study with active treatment in both arms and that the attrition rate in placebo-controlled studies is likely to be higher, sample sizes should be adjusted accordingly. Use of a noninferiority trial, which provides active treatment in both arms, may be an acceptable alternative to a placebo-controlled study, though a substantially larger sample size is required.

A negative correlation between the placebo effect and age has also been shown. Given a fixed therapeutic effect, a placebo-controlled trial of pediatric patients would therefore be more likely to fail (Weimer 2013). Indeed, a high placebo response was identified as a contributing factor for trial failure in studies of pediatric bipolar disorder (divalproex) and pediatric major depressive disorder (duloxetine) (Momper 2015). The potential impact of the placebo effect on study results should therefore be proactively considered and innovative trial designs to minimize placebo response, such as enrichment trial methodology, used when necessary.

Drug Delivery and Administration

Getting a drug into the body is one of the most commonly overlooked challenges of conducting a pediatric clinical pharmacology study (Abdel-Rahman 2007). In many cases, age-specific formulations are not readily available. Consequently, the existing formulation designed for adults must be physically modified (e.g., crushing a tablet), or a

pediatric formulation must be extemporaneously compounded for clinical use in pediatric patients. Children may also simply reject a medication for many reasons such as taste, smell, or texture, and the process of normal growth and development may create additional barriers by limiting absorption and bioavailability. The process of drug delivery and administration should therefore be carefully considered early in the study design process.

Formulation and Modification of Existing Dosage Forms

Oral liquid formulations, such as solutions and suspensions, are the standard for drug administration in children and allow accurate dose administration across the age spectrum. Solid oral dosage forms (e.g., tablets and capsules) are one of the simplest means to deliver medications but, in general, are not well managed or tolerated by most pediatric patients. Young children often cannot swallow solid dosage forms, and the ability to titrate the dose is limited, which is challenging in a population that varies substantially in size. Dry formulations such as chewable tablets, powders, and granules may be more tolerable with respect to swallowing, but they present their own challenges with respect to taste and texture. Like solid dosage forms, their use is also somewhat limited by an inability to titrate the dose.

When an age-appropriate formulation is not available, several dose administration strategies can be used (Abdel-Rahman 2007). Modifying an existing dosage form (e.g., crushing a tablet, opening a capsule, and dispersing in a small amount of food or drink immediately before administration; compounding an extemporaneous liquid formulation) is one of the most common mechanisms used to deliver medications when a pediatric formulation is not available. Several factors must be considered when modifying an existing dosage form for pediatric use. When mixing a crushed tablet or capsule contents with food, care must be taken to select a vehicle that does not alter the PK or PD of the drug product. Children may also refuse to take a crushed tablet or opened capsule that has been mixed with food because of an undesirable taste or texture. Care must also be taken to ensure that use of the modified formulation is consistent across the population being studied so that any potential formulation effects can be differentiated from those occurring as a result of differences in age.

When the adult formulation cannot be modified, it may be possible to evaluate the existing adult dosage form in children without modification (Abdel-Rahman 2007). When using a solid adult dosage form, the ability of the child to safely swallow a placebo tablet identical in composition and size to the solid adult dosage form should be assessed and verified during the screening or baseline phase of the study. The impact that restricting the formulation to just the solid adult dosage form will have on the number of eligible subjects and the balance of subject numbers in the various age cohorts

must also be weighed. Inability to titrate the dose may also lead to the administration of weight-corrected doses that exceed those labeled and approved for use in adults.

Palatability

Palatability is the primary factor influencing the administration of oral liquid formulations to children. Although children may accept a “one-time” dose of a poorly tasting liquid formulation, attempts at repeated administration may fail. To ensure effective drug delivery, issues of palatability should be addressed early in the study development process. Taste panels often consist of older children or adults. However, ontogenic taste profiles have been characterized with the recognition that sweet, salt, sour, and bitter flavors, together with affective responses to odor, develop at different ages (Lawless 1985). Formulation strategies used successfully in older individuals are therefore often ineffective in infants and young children. Multinational studies must also consider regional differences in preferred flavors and sweetness intensities (Abdel-Rahman 2007).

Developmental Alterations in Absorption

The process of normal growth and development can substantially alter drug absorption by its impact on the underlying processes influencing physicochemical behaviors at the site of drug entry (Abdel-Rahman 2007). The potential impact of development on drug absorption must therefore be considered during study design and development. For example, acid-labile drugs are more efficiently absorbed in the neonate and young infant for whom intragastric hydrochloric acid production is well below the concentrations for older children and adults (Huang 1953). Similarly, lipophilic medications that require solubilization in the intestine may have capacity-limited absorption in the neonate because of lower intraluminal bile salt concentrations (Abdel-Rahman 2007; Poley 1964). Drugs that undergo intestinal metabolism and those that depend on active transport pathways may also have altered bioavailability profiles, depending on the developmental expression patterns of those proteins.

The absorption of non-oral formulations may also be dramatically affected by developmental changes occurring across the age spectrum. Rectal formulations may be expelled more quickly because of an increase in the frequency of high-amplitude pulsatile contractions of the lower intestinal tract (Abdel-Rahman 2007). Similarly, transdermal formulations may be more efficiently delivered in preterm neonates because of a decrease in stratum corneum thickness and in full-term neonates and young infants because of improved hydration properties of the skin and a larger surface-to-volume ratio (Abdel-Rahman 2007).

Outcome Variables and End Points

Identifying measurable and meaningful outcome variables and end points is one of the greatest challenges in designing

a pediatric clinical trial. Although some information can be extrapolated from existing studies of adults, differences in pediatric biology and, in some cases, the disease process itself require that unique, age-specific end points be identified. A well-accepted end point in adults may therefore not be suitable for use in children, whose clinical presentation may dramatically differ. The failure rate for pediatric trials doubles when full extrapolation of adult efficacy to pediatric patients cannot be used (Dunne 2011). This underscores the importance of incorporating knowledge of the pediatric disease process and developmental biology into the clinical trial design. In addition to developmental considerations, the risk and invasiveness associated with various outcomes assessments must be considered, and end points must be selected that will minimize discomfort and maximize safety. For example, invasive techniques such as biopsies may be considered reasonable for adult research but are usually inappropriate for children. Tests that expose children to large amounts of radiation or that require significant blood sampling also require significant modification to reduce associated risks.

Age-Specific Normals and Reference Ranges

Given that many laboratory values and physiologic parameters change during the normal course of growth and development, it is important that age-matched reference ranges be used for assessing outcomes in the pediatric population. To determine a drug's effect on a given parameter, the impact of growth and development must also have been completely characterized so that the drug effect can be differentiated from any changes occurring as a result of the maturation process. This may not be true for many potential outcome indicators, however, especially those that are new or emerging such as novel disease markers or indices. Nevertheless, it is important to first understand what is “normal” so that the impact of a given drug on a disease process can be accurately assessed; therefore, ontogenic studies of healthy children may first be required before the end point can be used.

Age-Appropriate Monitoring Devices

To ensure the reliability and accuracy of outcomes data in pediatric clinical trials, it is important to use monitoring devices that are specifically designed for children and have been validated for use in this patient population. Use of devices that have not been developed for pediatric use will result in the generation of data that lack both sensitivity and accuracy and will significantly compromise the integrity of research results. More importantly, use of non-validated devices can result in inaccurate conclusions regarding drug safety and/or efficacy. The level of invasiveness of the device or methodology to be used should also be considered, using the least invasive assessment device, whenever possible (e.g., cheek swab vs. venipuncture for DNA collection).

Impact of Cognitive and Physiologic Development

Development is an important consideration in determining the methods for monitoring efficacy and safety outcomes. Assessments that depend on physical maturation, abstract thinking, or advanced cognitive concepts such as fluent verbal skills are often inappropriate for use in younger children. Age-specific differences in symptoms and an inability to self-report and accurately recall information are also challenges in this patient population. Furthermore, young children cannot express subjective symptoms such as pain, nausea, sedation, or dizziness; consequently, these and other subjective symptoms are often significantly underreported in nonverbal children (Abdel-Rahman 2007). Although visual scales (e.g., for pain) may be used, validating these scales is often difficult. Determining the degree to which the objective criteria reflect the subjective symptoms is also challenging.

Long-term Safety Assessment

Given the dynamic process of growth and development, some adverse events may not become apparent until much later in life. The adverse event profile may also differ in children and adults because of the differing effects of a drug on a developing system versus a mature system. In addition, a drug can affect both physical and cognitive growth and development. Incorporating long-term monitoring and surveillance into clinical studies whenever possible is therefore important to fully characterize possible drug effects on skeletal, behavioral, cognitive, sexual, and immune system maturation.

Measuring Drug Concentrations

The ability to accurately quantitate drugs and their metabolites in biological matrices is of critical importance for the successful conduct of pediatric phase I and II clinical trials. However, children present unique analytical concerns, and the need to account for physiologic variables must be considered within the framework of specific assay requirements. Analytical challenges must be addressed up front in the study design process, and validated assays should be in place before trial initiation.

Sampling Scheme, Analytical Issues, and Impact of Development

When developing a pediatric PK study, the sampling scheme should be carefully planned to obtain the most information from a minimum number of samples. Although data from studies conducted in adults may be useful to inform the sampling scheme, adult PK parameters do not account for maturational changes that can directly influence a drug's disposition profile. Consequently, the ability to draw meaningful conclusions from a sampling scheme created according to the adult PK profile is limited. Modeling and simulation are useful tools that can be used to develop age-appropriate

sampling schemes that optimize the information obtained from a limited number of samples. These approaches will be discussed later in the section entitled Modeling and Simulation.

Developmental differences between children and adults often result in unique analytical issues that can substantially affect the ability to obtain interpretable results. For example, the range of concentrations that an assay spans between the upper and lower limits of quantitation becomes an important experimental issue for drugs whose volume of distribution is expected to vary with age (Abdel-Rahman 2007). Age-related increases in distribution volumes, which occur most commonly with drugs that distribute in total body water, can result in terminal samples that fall below the lower limit of quantitation. In contrast, volume contraction can lead to peak concentrations that exceed the upper limit of quantitation. In both instances, the inability to accurately quantitate drug concentrations across the age spectrum leads to the exclusion of subjects that represent the population "extremes" and the reporting of biased mean PK parameters. Subsequent generalizations of the data will therefore be inaccurate.

Development can also significantly affect the "data-rich" segments of the plasma AUC profile, which in adults often occurs around the time of the maximum concentration (Abdel-Rahman 2007). Consequently, if a sampling strategy derived from adult PK data is applied to young children, there is a risk of completely missing the maximum concentration altogether because of a delayed rate of drug absorption in this pediatric age group. This phenomenon may also occur with extra-oral routes of administration such as intramuscular drug delivery, in which age-associated changes in capillary density may influence the absorption rate and ultimately the timing and magnitude of maximum plasma concentrations (Abdel-Rahman 2007). In addition to developmental influences on PK, the presence of any age-specific endogenous substances that can interfere with planned quantitative methods should be considered. For example, when planning quantitation of both free and total drug concentrations, alterations in the binding affinity of proteins for a given drug substrate, together with circulating displacers in young children, may alter the free fraction of a drug. Many of these same factors can also compete for elimination pathways and influence the clearance rates of drugs that share a common route of elimination.

Allowable Blood Volumes

Blood sampling requirements are one of the most common physiologic constraints associated with pediatric clinical pharmacology studies, and both the volume and the frequency of sampling are often of concern. Most regulatory guidance documents defer to local IRBs or independent ethics committees to define the amount of blood that can be obtained for research purposes, and the FDA has released no specific guidelines for allowable sampling volume and frequency.

Table 2-2. Age Ranges and Corresponding Volume Limits for Pediatric Blood Sampling

	Whole blood volume (mL/kg)	Mean body weight (kg)	Whole blood volume (mL)	3% (mL)	1% (mL)
Newborn, 1 day	83	3.45	287	8.6	2.9
Infant, 3 months	87	6.15	535	16.1	5.4
Infant, 6 months	86	7.85	675	20.3	6.7
Infant, 12 months	80	10.1	808	24.2	8.1
Children, 6 years	80	20.6	1648	49.4	16.5
Children, 10 years	75	32.6	2445	73.4	24.5
Adolescent, 15 years	71	54.3	3855	115.7	38.6

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The European Medicines Agency recommends that blood sampling volume related to a trial not exceed 3% of the total blood volume over 4 weeks and not exceed 1% of total blood volume at any one time (Table 2-2). Similarly, the WHO recommends that a maximum of 3 mL/kg within 24 hours be allowed for blood sampling in children involved in clinical research and recommends even lower limits for critically ill children (Howie 2011). This is consistent with the requirements of most IRBs, which, in general, stipulate that no more than 3% of the estimated circulating blood volume can be collected for research over 2–8 weeks. Institutional review boards also consider the amount of blood required for standard medical care during the study participation period and how the additional volume collected for research will affect the risk-benefit ratio. When considered in the context of weight and circulating blood volume, allowable sample volumes can be restrictive, amounting to less than 5 mL in the premature neonate.

The volume and frequency of blood sampling can be minimized using micro-volume assays (volume), dried blood spots (volume), and sparse sampling techniques (frequency, discussed later in the chapter in the modeling and simulation section. Modern assay techniques also allow the use of small sample volumes to determine drug concentrations, but data quality may be affected if the sample volume is insufficient to allow for reanalysis when required (DHHS 2014).

CONDUCTING PEDIATRIC STUDIES

Although study design is critical in determining the success of a pediatric clinical study, the best clinical study cannot successfully be executed without adequate infrastructure to support the trial. Consequently, care should always be taken to ensure that the necessary resources, infrastructure, and personnel are available before initiating any study. Implementing a pediatric study requires that the age-specific requirements of the population be accounted for and attended

to throughout the study. Anticipating the unique needs of children participating in clinical studies should also be a priority.

Infrastructure and Personnel

Lack of infrastructure and trained personnel is one of the greatest challenges to successfully conducting a pediatric clinical pharmacology study. Consultation with experts should always be sought in study development, implementation, and analysis. Experts with knowledge and a working understanding of pediatric therapeutics, pediatric clinical trial methodology, and physiologic development are critically important in designing and carrying out a trial that is both feasible and scientifically valid. Research personnel (e.g., nurses, clinical research coordinators, laboratory technicians) with training and experience in working with children and in performing pediatric procedures are also important to ensure that specimens and data are collected and analyzed accurately. Availability of a research environment that is “child-friendly” and includes areas such as a playroom where children can go during extended study visits and receive age-appropriate food is imperative. The research environment should also be non-threatening and, if possible, should have designated areas for invasive procedures such as blood sampling.

Research Consortia and Data Sharing

Research networks provide an opportunity to bring together different areas of expertise in pediatric therapeutics; several of these networks have already been developed. There are over 80 pediatric clinical research networks in the United States and Canada and over 60 in the EU, several of which focus specifically on pediatric clinical pharmacology trials (AAP 2016). The U.S. Pediatric Trials Network was founded in 2010 to conduct pediatric trials for off-patent drugs in which PK, safety, and/or efficacy data are lacking. The Medicines for Children Research Network, created in the Netherlands in

2008, also focuses on conducting well-designed studies of pediatric therapeutics and consists of a coordinating center, local research networks, clinical studies groups, and a neonatal network. The Global Research in Paediatrics network is an EU-funded initiative aimed at linking over 1000 institutions to provide an international infrastructure to stimulate and facilitate the development and safe use of medicines in children. This network also plans to develop guidelines for pediatric research and to provide training in pediatric clinical pharmacology.

In addition to increasing clinical trial infrastructure, the ability to share patient-level clinical trial data between investigators has become increasingly important. Data sharing allows for the validation of PK/PD models using data sets other than those used to create the model. It also allows for subgroup analysis of data from children enrolled in adult trials and meta-analyses of pediatric data. Sharing data facilitates the creation of interinstitutional collaborations, which in turn further strengthens the infrastructure to support pediatric clinical trials (Sampson 2012).

Subject Identification and Recruitment

Given the complexity of pediatric research, it can be challenging to identify and recruit subjects for clinical studies. From a logistical perspective, identifying a sufficient number of children may be difficult because the number of children with any given disease is often small. Many trials also compete for the same population of children, further complicating the ability to meet enrollment goals. From a parent's perspective, practical issues such as the amount of time involved, number of study visits required, and time and distance required to travel to the study site can affect the decision to participate. Confidentiality, perceived risk, requirement for painful or invasive procedures, and ethical concerns (discussed in depth in a separate chapter) are also common reasons for declining participation. Care should therefore be taken to develop studies that are practical, reasonable, and "child-friendly."

The process of identifying and recruiting subjects should conform to the standard principles governing the responsible conduct of research in human subjects and should be conducted in a manner that is free from inappropriate inducements to the parent, legal guardian, and/or study participant. Reimbursement for time, travel, and meals may be provided, though any compensation should be reviewed and approved by a local IRB or ethics committee. When developing a recruitment strategy, every attempt should be made to include individuals representing the demographics of the regions and disease(s) being studied and to identify potential sites with pediatric expertise and access to eligible subjects. Creativity and initiative are also integral to successfully identifying, enrolling, and retaining study subjects, and a strategy that involves a combination of tactics, such as flyers, media advertisements, and educational brochures, is often most successful. An understanding of the motivation of children

and their parents within the target study population to participate (e.g., contribute to science, help others) is also important for developing a successful recruitment program.

INTERPRETING AND ANALYZING DATA FROM PEDIATRIC STUDIES

When analyzing and interpreting data from pediatric clinical pharmacology studies, several factors must be considered in order to avoid making incomplete and/or incorrect conclusions regarding study data. Given the dynamic nature of and wide diversity in the pediatric population, the data analysis plan should allow for consideration of potential covariates that may influence interpretation of study results. Examples of such covariates include age, body weight, body surface area, gestational age and birth weight (neonates), race, ethnicity, sex, and results from relevant laboratory tests (DHHS 2014). In addition, concomitant and recent drug therapy should be recorded and their impact on study outcomes considered. If DNA is available, the potential impact of genetics on study end points and outcomes should also be explored, when feasible.

Data Normalization for Weight and Dose

Body weight or size is among the most important covariates that can influence results from pediatric trials. This is particularly true for studies designed to characterize the PK of a drug or biologic agent. When making comparisons within and between populations that differ significantly in size and/or body composition, failure to account for these differences can lead to inappropriate or inaccurate conclusions. Consequently, the contribution of weight or body surface area to PK variability should always be assessed (DHHS 2014). When using a fixed-dose design (i.e., every subject receives the same absolute milligram dose), PK parameters should be considered within the context of the weight (milligram per kilogram) or surface area (milligram per square meter) corrected dose. This is because administering a fixed dose to children of different ages and weights can produce a span of weight-corrected (milligram per kilogram) doses and systemic drug exposures. As such, a larger child administered the same absolute dose as a smaller child will have lower exposure estimates in response to what is essentially a smaller weight-adjusted dose. Weight normalization of the dose is therefore required before data analysis (Abdel-Rahman 2007). Dose correction may also be required in some situations. For example, when body weight or size varies dramatically between age cohorts, exposure estimates (e.g., C_{max}, AUC) must be corrected for dose when using a fixed-dose study design. Adjustment of exposure estimates for dose is also required when evaluating the relationship between drug exposure and genetics to avoid making inaccurate assumptions about potential gene-dose effects (Abdel-Rahman 2007).

Developmental Considerations

Weight and body size are often used as a surrogate of physiologic development or maturation. Adjusting PK parameter estimates for weight is therefore standard practice in many pediatric clinical pharmacology studies. Failure to weight-correct PK parameters may lead to conclusions that do not accurately reflect the role of maturation on drug bio-disposition and result in reports of relationships that either do not exist or would not be as strong had weight initially been considered (Abdel-Rahman 2007). This is particularly true in populations such as neonates, in whom the organs responsible for drug clearance are maturing in parallel with physiologic growth and development. In this population, there will likely be a very strong relationship between PK parameters such as uncorrected total body clearance and distribution volume by age because both age (development) and weight (growth) are nested within each PK parameter. To determine whether there is a true age effect, correction of the parameters for weight is therefore required.

OVERCOMING THE CHALLENGES OF PEDIATRIC RESEARCH

The many barriers to conducting research in children have historically limited the information available for drug labeling and clinical decision-making in the pediatric population. Recent initiatives have focused on overcoming rather than accepting the challenges to conducting research in children and have resulted in several novel and innovative strategies that have been successfully applied in pediatric trials. There is also an increased awareness of the need to create evidence-based guidelines for developing and conducting clinical trials in children to ensure that studies are rigorous, scientifically valid, and of sufficient quality to support drug labeling and clinical decision-making. These advances will be briefly discussed in the sections that follow.

Evidence-Based Guidelines for Pediatric Clinical Trials

Pediatric clinical trials often have shortcomings that compromise the ability to draw meaningful conclusions and that, in many cases, result in trial failure. The quality of clinical research is also substantially lower in children than in adults for reasons discussed previously. There is a significant need to develop practical and evidence-based guidance to improve the reliability and relevance of pediatric clinical trials. Standards for Research in Child Health, an initiative involving about 180 experts from industry, academia, and regulatory agencies across the world, was founded in 2009 to begin addressing this need (Hartling 2012). The mission of Standards for Research in Child Health is to “improve the design, conduct and reporting of pediatric research through the development and dissemination of evidence-based standards.” To date, this group has completed a systematic review of available pediatric clinical research guidelines and has created a list of 11 priority issues

for which development of evidence-based guidance documents is needed. Of these, six are pediatric-specific and include recruitment and consent, outcome measures, appropriate age groups, age-specific dosage, age-specific medication administration, and pediatric trials in developing countries. The other five issues are generic trial design issues related to sample size, data monitoring committees, risk of bias, relevant comparators, and safety.

To date, Standards for Research in Child Health has published 6 of the 11 planned standards, each of which contains specific practice recommendations (Hartling 2012). Standard 1 (recruitment and consent) focuses on ethical considerations with the consent process and provides recommendations addressing child and guardian objection to research participation, equitable recruitment, compensation for participants, and the need to differentiate research participation from clinical care (Sampson 2012). Standard 2, containing risk of bias, focuses on design and reporting practices intended to improve the quality of evidence resulting from pediatric trials. Standard 3, data monitoring committees, provides straightforward recommendations regarding needs and scope in pediatric studies. Standard 4 provides recommendations regarding sample size and emphasizes a priori sample size determination and inclusion of statisticians during the design phase. Standard 5, outcomes in children, underscores the need for population-specific clinical trial end points, and standard 6, age groups for pediatric trials, highlights the standardization of pediatric age groups used in clinical trials.

Innovative Trial Design

Recent innovations in pediatric clinical trial design have been developed and integrated into studies to successfully overcome some of the most common challenges associated with conducting research in children. Novel strategies that directly address sampling limitations (frequency and volume), analytical issues, and subject availability have significantly improved the ability to collect and analyze data from pediatric subjects, particularly neonates. Application of modeling and simulation techniques and the emerging science of pharmacometrics have also been increasingly used to inform the design and conduct of pediatric trials.

Sparse and Scavenge Sampling

Traditional PK studies require the collection of several (10–15) high-volume (greater than 3 mL) samples per subject. This intensive sampling approach is not feasible in infants and young children, given their significantly reduced blood volume compared with adults. Sparse and scavenge sampling approaches are increasingly used to reduce the overall sample volume needed for pediatric clinical pharmacology studies (Table 2-3). Compared with traditional PK sampling methods, sparse sampling uses fewer samples per patient (2 or 3 vs. 10–15) and requires a much smaller sample volume.

Table 2-3. Comparison of Sampling Techniques

Method	Pros	Cons
Sparse sampling	• Lower number of samples per patient • Small sample volume	• Typically must be used in combination population PK methods
Scavenge sampling	• Small sample volume • Reduced sampling burden • Eliminates need for study-specific blood sampling • Potentially increased consent rates	• Dependent on availability of residual samples • Potential drug stability issues • Unsuitability of collection times for PK analysis • Reduced accuracy of collection time recording • Low sample volumes
Dried blood spots	• Obviates need for plasma extraction • Low sample volume requirement • Samples can be stored at room temperature • Simple bioanalytical analysis	• Potential for matrix-dependent PK parameters given that some drugs concentrate in blood cells

PK = pharmacokinetics.

This strategy has been successfully applied to characterize the PK of several antimicrobial agents in neonates and young children (Laughon 2011). Most often, sparse sampling is used together with population PK (discussed in the section that follows). However, this approach was also used to successfully characterize steady-state PK in a recent pediatric therapeutics trial of micafungin, supporting the expansion of its use in future trials (Laughon 2011).

Similar to sparse sampling, the scavenged sampling approach reduces the sampling burden required for pediatric PK studies. Scavenged sampling relies on the use of residual or “waste” blood or plasma samples left over after completing laboratory tests done as part of standard medical care. This approach is particularly attractive for children, given that it eliminates the need for venipuncture for study-specific sample collection and offers the potential to collect several samples per subject. Scavenged sampling also offers the potential to increase consent rates because it eliminates the need for sample collection. Potential limitations of the scavenged sampling approach include issues with drug stability, collection times that are unsuitable for PK analysis, reduced accuracy in sample collection time recording, and low sample volumes. However, many of these limitations can be overcome by having several samples available per subject and applying modeling and simulation techniques estimating population PK parameters (discussed in the following).

Dried Blood Spot Sampling

Dried blood spot sampling has emerged over the past few years as a novel sampling method that offers significant advantages for use in pediatric clinical pharmacology studies. This method, which involves collecting 15–30 mm³ of whole blood by finger or heel stick on blotting paper, has been used in newborn metabolic screening for over 5 decades but

has only recently been applied in pediatric trials. Dried blood spot sampling obviates the needs for extracting plasma and training personnel in sample processing. Other advantages include a low sample volume, ability to store samples at room temperature, and simple bioanalytical analysis (Laughon 2011). Given that some drugs concentrate in blood cells, however, there could be matrix-dependent PK parameters, which should be considered.

Multidrug Assays

Advances in technology provide the capability to measure drug concentrations in ultra-low sample volumes (less than 100 mm³). Optimization of high-performance liquid chromatography–based analytical methods and incorporation of mass spectrometry techniques into sample analysis have also facilitated the simultaneous measurement of several compounds in the same low-volume sample (Laughon 2011). This multiplex assay approach is particularly useful in children because they are often treated concurrently with several drugs. Using a single multiplex assay also increases clinical trial efficiency by measuring concentrations of all administered agents without the need to develop and validate several individual assays specific for each drug (Laughon 2011).

Opportunistic and Pragmatic Studies

Integrating research into standard clinical care in an opportunistic manner can generate useful information that can in turn be used to support drug labeling and clinical decision-making. These opportunistic or pragmatic trials use children in routine practice settings who are receiving a drug as part of standard medical care and rely on standard-of-care drug administration rather than a study-specific protocol. After obtaining informed consent, information is collected from electronic health records or other data sources and assessed

accordingly. Blood samples may also be collected at the time of routine laboratory tests, scavenged, or collected using a study-specific sparse sampling approach. The opportunistic or pragmatic trial approach has been used to generate meaningful PK data in pediatric populations and to inform the design of phase I–III pediatric clinical trials (Laughon 2011). Given the advantages of this approach with respect to subject identification, recruitment, and consent, the number of opportunistic and pragmatic studies will likely continue to increase as the demands for pediatric data continue to rise.

Pharmacometrics/Modeling and Simulation

Modeling and simulation are quickly becoming an integral part of pediatric clinical pharmacology studies and have played an important role in optimizing the design and conduct of PK trials in children (Figure 2-2). Drawing on data from studies of adults and older children, *in silico* and other modeling methods can be used to generate preliminary data that can in turn be used to inform trial development. For example, developed models can be used to determine the required sample size and optimal sampling scheme for a given trial before initiating a study. Models can also be used to more accurately estimate the dose required for a given age cohort to achieve a target level of exposure because they account for differences in body size, elimination pathways, and known developmental changes. Consequently, the FDA has set a goal to have all pediatric study designs submitted

in response to a written request supported by modeling and simulation by 2020 (FDA 2015).

Several different types of models have been used successfully to support pediatric trials. Physiologically based PK modeling uses the anatomic and physiologic structure of various organs in the body to model and predict drug disposition and tries to incorporate maturational changes in liver mass, organ blood flow, and enzymatic activity (Laughon 2011). Consequently, PBPK models can predict drug exposure in different age groups and guide optimization of the dosing schedule and sampling times. They can also support risk assessment by investigating possible drug interactions and the impact of organ dysfunction. Physiologically based PK modeling has been used in pediatric drug development to plan a first-time-in-pediatrics study, optimize study design, verify the model in specific age groups, recommend starting doses, inform enzyme ontogeny using a benchmark drug, and facilitate covariate analysis for effects of organ dysfunction or drug interactions in pediatric patients (DHHS 2014).

Population PK models are another type of clinical trial simulation commonly used in pediatric studies. With population PK, samples are attributed to a population rather than an individual, and the model captures the time course of concentration versus response at the population level. Population PK models can be used for simulations to support dose selection and study design and to extrapolate information from adults to children. Analysis of sparse sampling data collected

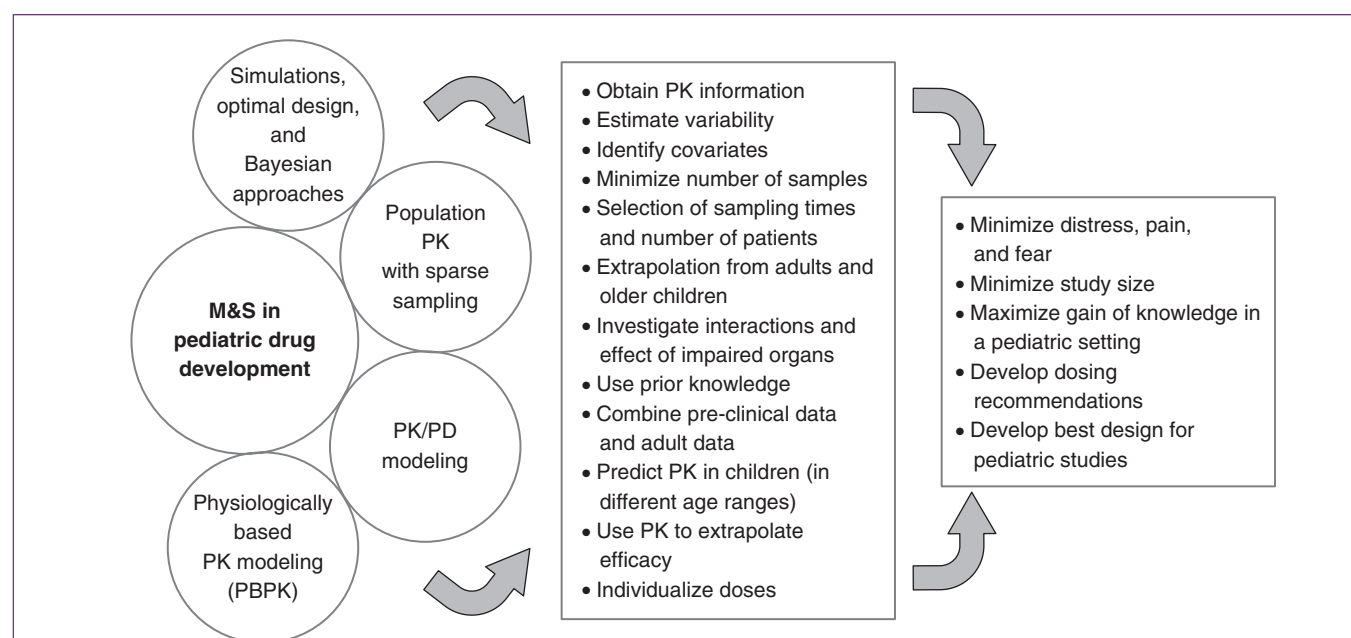


Figure 2-2. Modeling and simulation in pediatric drug development.

M&S = modeling and simulation; PK = pharmacokinetics.

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in pediatric studies, with or without PBPK modeling, is also being increasingly adopted and endorsed by regulatory agencies (FDA and European Medicines Agency) and industry.

Pharmacometrics, also known as quantitative clinical pharmacology, further expands the capabilities of modeling and simulation using quantitative models encompassing physiology, pharmacology, and disease progression to describe PK/PD behavior over time in patients in relation to both therapeutic and adverse effects (Vinks 2015). Pharmacometrics is routinely used to make decisions about sample size, PK and PD sampling points, and end point selection as well as provide supportive evidence of effectiveness, dose, and dosing regimen selection. This quickly expanding science is also being increasingly used to make regulatory decisions regarding pediatric drug approval and has drastically improved the ability to achieve targeted exposure by selecting age-appropriate doses and using dose adaptation rules.

CONCLUSION

Children are large consumers of medications, and the expanding use of drug therapy in the pediatric population continues to support the need for high-quality data to support age-specific labeling. Although legislative initiatives over the past 2 decades have resulted in a significant increase in the number of pediatric clinical trials, many of these trials fail to provide meaningful or useful information because of fundamental flaws in study design that fail to account for the unique and dynamic nature of the pediatric age spectrum. It is therefore imperative that pediatric studies be designed in such a way to ensure the generation of rigorous and scientifically valid data that can in turn be used to support labeling and clinical decision-making.

Conducting research in children certainly has its challenges. However, advances in the sciences of clinical trial methodology, analytical chemistry, and pharmacometrics have provided unique and creative ways to overcome these challenges. Creation of national and international infrastructure to support the conduct of pediatric clinical trials by developing multi- and cross-disciplinary research consortiums and networks has also greatly improved the ability to successfully conduct large-scale pediatric studies on a multinational scale. Continued development and refinement of evidence-based guidelines for the conduct of pediatric clinical trials will also further strengthen the pediatric clinical trial enterprise and continue to move the discipline toward its ultimate goal of safe and effective therapeutics for children of all ages.

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Self-Assessment Questions

Questions 21 and 22 pertain to the following case.

A pharmaceutical company proposes the DERMATE study to evaluate the safety, tolerability, and systemic exposure to a new ointment formulation of a topical agent for atopic dermatitis in children age 1–6 years. The agent is not yet commercially available. After applying a topical anesthetic cream, the DERMATE study proposes to collect blood samples (8 mL per sample) by direct venipuncture on study days 1, 7, and 14 at the following times: baseline and 2, 4, 6, 8, and 12 hours after ointment application. Whole blood samples will be frozen immediately after collection and will be used to determine concentrations of the parent drug using a validated analytical method with a lower limit of quantification of 0.3 ng/mL. All analyses will be shipped to a centralized laboratory for analysis. An overnight stay will be required the night before drug administration/PK sampling, and all DERMATE study procedures will be done in the pediatric clinical research center.

21. Which one of the following is of most concern with respect to the DERMATE proposed blood sampling scheme?
 - A. Frequency of sample collection
 - B. Volume of blood collected
 - C. Method of collection
 - D. Experience of personnel collecting sample
22. Which one of the following innovative trial methods has the most potential to improve the proposed DERMATE study protocol?
 - A. Opportunistic study design
 - B. Scavenge sampling
 - C. Dried blood spot sampling
 - D. Multidrug assays
23. You wish to study an antibiotic in the pediatric population that was recently approved for the treatment of sepsis in adults. After a search of the literature, you determine that the course of infection and response to the drug should be similar in adults and children. However, the exposure-response relationship in children is not well described, and there are currently no clinical biomarkers to predict efficacy in the pediatric population. Which one of the following approaches is most appropriate for this study?
 - A. Full extrapolation
 - B. Partial extrapolation without efficacy studies
 - C. Partial extrapolation with efficacy studies
 - D. No extrapolation
24. A study uses the full extrapolation approach. In which one of the following pediatric age groups is the study most likely to be successful in establishing safety and efficacy?
 - A. Neonates
 - B. Infants
 - C. Children
 - D. Adolescents
25. A fixed-dose study comparing systemic drug exposure uses weight normalization of doses. In which one of the following age cohorts are the study data likely to be most accurate?
 - A. Neonates
 - B. Infants
 - C. Children
 - D. Adolescents
26. A study proposes to evaluate the single-dose PK of an orally administered antiepileptic agent in children age 6 months to 5 years from several centers. Given that a liquid formulation is not available, the sponsor provides instructions for preparing a suspension that will be administered as part of the clinical trial. A centralized laboratory analysis of samples at the end of the study shows that over half of the samples from a single site have post-peak concentrations below the lower limit of quantitation of the analytical assay. Which one of the following is the most likely explanation for this observation?
 - A. Inadequate assay sensitivity
 - B. Incorrect protocol study dose
 - C. Batch variability in drug concentration
 - D. Inadequate assay specificity
27. You wish to study the efficacy of a new migraine drug in children age 12–16 years. Existing data show that the pathogenesis of disease and response to treatment are similar in adult and pediatric patients, but that the duration of migraine attacks is shorter in children than in adults. Given this information, which one of the following study designs would be most appropriate?
 - A. Placebo-controlled trial with assessment of efficacy at 1 hour post-dose
 - B. Placebo-controlled trial with assessment of efficacy at 4 hours post-dose
 - C. Comparator-controlled trial with assessment of efficacy at 1 hour post-dose
 - D. Comparator-controlled trial with assessment of efficacy at 4 hours post-dose

28. A sponsor submits an application to the FDA to study the PK, safety, and efficacy of an α_1 -receptor antagonist for a disease that has no clinical correlate in adults. Which one of the following would be the most effective dose selection strategy for the planned pediatric studies?
 - A. Determine the tolerated pediatric dose range, and study several doses across this range.
 - B. Use PBPK (physiologically based pharmacokinetic modeling) to estimate the dose needed to achieve a level of exposure shown to be effective for a similar disease in adults.
 - C. Use the principles of allometric scaling to determine the fraction of the adult dose needed to achieve the level of exposure shown to be effective for a similar disease in adults.
 - D. Use the principles of developmental pharmacology to determine the weight-normalized dose needed to achieve the level of exposure shown to be effective for a similar disease in adults.
29. A study evaluates the efficacy of a new antihypertensive agent using a commercially available, adult home ambulatory blood pressure monitoring device. In which one of the following age groups would this study be most appropriate?
 - A. Neonates
 - B. Infants
 - C. Children
 - D. Adolescents
30. In which one of the following pediatric age groups would derivation of a sampling scheme from adults be most appropriate for studying the PK of a drug administered by intramuscular injection?
 - A. Neonates
 - B. Infants
 - C. Children
 - D. Adolescents
31. Which one of the following approaches would be most appropriate for a drug in which the disease and intervention behave similarly in adults and children and the exposure-response relationship is comparable in adult and pediatric patients?
 - A. Full extrapolation
 - B. Partial extrapolation without efficacy studies
 - C. Partial extrapolation with efficacy studies
 - D. No extrapolation
32. Stratification of children by which one of the following parameters would be most appropriate for analyzing data from a PK study conducted in adolescents?
 - A. Chronological age
 - B. Tanner stage
 - C. Weight
 - D. Circulating sex hormone concentrations
33. A study proposes to analyze the safety, PK, and efficacy of an intravenous proton pump inhibitor for the treatment of gastroesophageal reflux in infants. Infants with suspected reflux, determined on the basis of clinical symptoms, will be eligible for inclusion. The study requires that children fast for 24 hours before administration of the study drug. Blood samples (0.25 mL) will be collected by heel stick at baseline, 4, 8, and 12 hours for PK analysis. Continuous monitoring of esophageal pH is also required in all infants undergoing the procedure as standard medical care for confirmatory diagnosis. Which one of the following is of most concern with respect to this proposed study design?
 - A. Continuous esophageal pH monitoring
 - B. Heel-stick blood collection method
 - C. Blood sample volume
 - D. 24-hour fasting requirement
34. In which one of the following situations with similar disease progression would full extrapolation of efficacy data from adults be most appropriate?
 - A. Similar exposure-response relationship
 - B. Undefined response to treatment in children
 - C. Undefined exposure-response relationship in children
 - D. No PD measurements to predict efficacy in children
35. Which one of the following best describes a study design that relies on standard-of-care drug administration rather than a study-specific protocol?
 - A. Pharmacometrics
 - B. Opportunistic
 - C. Population PK
 - D. Physiologically based PK
36. Which one of the following strategies would be most effective in reducing the sample volume required for PK analysis?
 - A. Sparse sampling
 - B. Population PK
 - C. Micro-volume assays
 - D. Pharmacometrics modeling
37. Which of the following strategies would be most appropriate to overcome sampling limitations in a pharmacokinetic study of a single drug in neonates?
 - A. Traditional sampling
 - B. Sparse sampling
 - C. Scavenge sampling
 - D. Multiplex assay

38. In which one of the following FDA-defined pediatric age cohorts would a subgroup analysis of PK data based on the known ontogenic patterns of drug-metabolizing enzymes be most beneficial?
- A. Neonates
 - B. Infants
 - C. Children
 - D. Adolescents
39. Data analysis from a PK study shows that the average C_{max} of a drug is 3-fold higher in children receiving a solid tablet dosage form than in those for whom the tablet was crushed and mixed with apple juice. Further analysis of the data shows that the presystemic clearance of the drug is significantly greater in children receiving the crushed form than in those receiving the solid tablet. Which one of the following is the most likely reason for this observation?
- A. Incomplete administration of crushed tablet
 - B. Poor drug solubility in apple juice
 - C. Drug-apple juice interaction
 - D. Direct effect of apple juice on drug absorption
40. Which one of the following would best determine the efficacy of a new opioid analgesic in previously healthy young children age 4–6 years?
- A. Observational report by a behavioral scale (e.g., FLACC [Face, Legs, Activity, Cry, Consolability])
 - B. Self-report by the Wong-Baker FACES Pain Rating Scale
 - C. Self-report by a visual analog scale
 - D. Self-report by a numeric rating scale

Learner Chapter Evaluation: Study Design in Pediatrics.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

18. The content of the chapter met my educational needs.
19. The content of the chapter satisfied my expectations.
20. The author presented the chapter content effectively.
21. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
22. The content of the chapter was objective and balanced.
23. The content of the chapter is free of bias, promotion, and advertisement of commercial products.
24. The content of the chapter was useful to me.
25. The teaching and learning methods used in the chapter were effective.
26. The active learning methods used in the chapter were effective.
27. The learning assessment activities used in the chapter were effective.
28. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

29. Justify when a pediatric study is scientifically necessary and when extrapolation from adult data is valid.
30. Evaluate design issues unique to pediatric drug studies for each age category (neonates, infants, children, and adolescents).
31. Design a clinical study for a child of any age.
32. Apply the principles of developmental pharmacology in the design, conduct, and interpretation of pediatric studies.
33. Develop and apply strategies for overcoming the challenges of conducting clinical trials in children.
34. Judge whether a research protocol is appropriate for conduct in a child of a given age.
35. Please provide any specific comments related to any perceptions of bias, promotion, or advertisement of commercial products.
36. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

Database Research in Pediatrics

By Donald Klepser, Ph.D.; and Gary L. Cochran, Pharm.D., S.M.

Reviewed by Drew Roberts, Pharm.D., Ph.D.; Courtney Sutton, Pharm.D., BCPPS; and Brent A. Hall, Pharm.D., BCPPS

LEARNING OBJECTIVES

1. Analyze the different types of database resources available for database research.
2. Evaluate the advantages and disadvantages of database research.
3. Estimate the impact that confounding has in the practice of database research.
4. Evaluate common study designs used in database research and assess their impact on interpretation of study results.
5. Design a plan that will assist the researcher in preparing to conduct pediatric database research.
6. Justify the use of popular pediatric databases and the information they contain for research.

ABBREVIATIONS IN THIS CHAPTER

ACE	Angiotensin converting enzyme
AHRQ	Agency for Health care Research and Quality
CHIP	Children's Health Insurance Program
CPT	Current procedural terminology
DRG	Diagnosis-related group
ELSO	Extracorporeal life support organization
EMR	Electronic medical record
ICD	International Classification of Disease
MEPS	Medical expenditure panel survey
MSIS	Medicaid Statistical Information System
MUE	Medication use evaluation
ONC	Office of the National Coordinator
NAMCS	National ambulatory medical care survey
PBM	Pharmacy benefits manager
PHI	Protected Health Information
PHIS	Pediatric Health Information System
RCT	Randomized controlled trials
ROC	Resuscitation Outcomes Consortium
VON	Vermont-Oxford Network

[Table of other common abbreviations.](#)

INTRODUCTION

The paucity of data available through formal pediatric clinical research studies can present unique challenges to caring for pediatric patients. Although it is often perceived that randomized, placebo-controlled studies should guide an evidenced-based approach to practice, the logistics of such research is often not practical or ethical. Researchers must often rely on existing adult data or from small pediatric studies to create standards of pediatric care and clinical pediatric guidelines. Due to recent advances in information technology, database research has become an avenue for unequivocal access to existing medical information. This information is available through a variety of sources, including electronic medical records, insurance claims databases, disease registries and national surveys, such as the National Ambulatory Medical Care Survey (NAMCS) or Medical Expenditure Panel Survey (MEPS). Researchers have only recently begun to capitalize on the rich data sources that are available. The application of existing health data in the pediatric patient population for research purposes serves as a great opportunity for future data collection and data mining.

This chapter defines database research, identifies different types of databases, reviews database research methodologies, explores the application of such methodologies in the pediatric population, describes the challenges inherent to pediatrics, and presents potential solutions to overcoming these barriers. The information in this chapter serves as a platform for more clinicians and researchers to use databases to help address the clinical challenges facing this unique patient population.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of the use of claims for billing of health care services provided.
- General understanding of pediatric clinical disease states.
- Baseline knowledge of clinical research design and statistics.

[Table of common laboratory reference values.](#)

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Cadarette SM, Wong L. [An introduction of health care administrative data.](#) Can J Hosp Pharm 2015;68:232-7.

DATABASE RESEARCH

Definition of Database Research

Database research is a field of research that uses existing sources of data to examine health outcomes, patient behaviors, and patterns of health care service use. Database records can be obtained from a variety of sources, including insurance enrollment files; insurance claims data for outpatient, inpatient, emergency, and prescription services; electronic health records; and national survey data. It is important to remember that most databases were not created for the purposes of research; rather, to facilitate billing and payment of health care-related services and to monitor and/or analyze the effective use of health care resources. Thus, the researcher may find it difficult to find and decipher the information needed to answer the clinical question. There remains considerable data to evaluate the real world utilization patterns of health care resources as long as the researcher understands the limitations of these data and that the proposed research methodology does not “over-reach” the data that is available.

Insurance Claims Data

Enrollment Files

Enrollment files are an insurer’s record of members who have coverage for a specified time. Key data elements associated with enrollment files include demographic information, such as age and sex, and geographic information, such as county of residence. Enrollment files also contain insurance plan coverage that can illustrate gaps in coverage. Plan design variables are also available to highlight the difference in coverage for enrollees. This can include the patient cost-sharing structure and the provider networks among other information.

Thus, if a researcher wishes to examine potential health care disparities caused by coverage gaps or differences in patient out-of-pocket (OOP) costs, enrollment files can serve as an excellent data source.

Medical Claims

Medical claims data allow researchers to observe when and what specific type of insurance-covered health care services were provided to patients in outpatient, inpatient, and emergency settings. These records also contain diagnostic information that facilitates tracking of disease incidence and prevalence. Medical claims are composed of two distinct databases, institutional and provider, both of which are based upon reimbursement for health care services that have been provided. Institutional (e.g., hospital) claims are reimbursed based upon an episode of care, whereas providers (e.g., physicians, physical therapists) are reimbursed upon the professional procedure that was performed.

Institutional claims are reimbursed upon the diagnosis-related group (DRG) system of about 500 groups, in which payment is provided after the care of service has been provided. Reimbursement rates are determined prospectively for each DRG through negotiations between the institution and the insurance company. A unique claim identifier, an institutional identifier, and admission and discharge dates accompany the DRG claim. Additional information that is available to the researcher includes up to 10 diagnoses using International Classification of Disease (ICD) codes (either ICD-9 or ICD-10), procedures performed either through documented ICD codes or other standardized codes (e.g., Current Procedural Terminology [CPT]), and costs associated with the encounter. Costs are further divided into total costs, which includes both costs to the patient, as well as to the insurer.

Provider claims are submitted by health care providers, which are not included in institutional claims. Physicians, nurse practitioners, physician assistants, and other allied health professionals (e.g., occupational and physical therapists) submit claims on the procedure level using CPT codes. The American Medical Association has developed the CPT codes as a way of organizing diagnostic, medical and surgical procedures. Pharmacists, generally, are not able to utilize CPT codes for clinical services provided within an institution, such as a hospital, because most insurers believe that the costs associated with “clinical pharmacy services” are captured in the reimbursement of the medications used. Pharmacists are able to utilize CPT codes on an outpatient basis, independent of prescription claims. Information available to researchers through provider claims data are very similar to institutional claim data, including unique provider and encounter identifiers, service dates, types of procedures, and costs. When used together, provider and institutional claims allow researchers to capture an entire episode of care across providers and settings. They can also provide valuable information on health care utilization and outcomes over time.

Prescription Claims

Prescription claims data provide records of insurance payments for prescription fills and allows researchers to observe prescribing behaviors, patients' medication utilization patterns, medication adherence and drug cost trends. Information obtained from the prescription claim includes unique patient and claim identifiers, prescription service date, drug name/identifier, dose, days supplied, and costs. Prescription claims are distinctly different than institutional or provider claims. Whereas institutional and provider claims are adjudicated after the care or procedure has been performed, prescription claims are adjudicated before dispensing. Prescription claims alone can be used to evaluate utilization and adherence to therapies, but when they are used in conjunction with medical claims, they can provide a reasonably complete picture of a patient's care and outcomes.

Medical Records

Medical records, including electronic medical records (EMR), are the record of care provided to patients and captured in the patient's chart. Medical records research provides another data-rich environment to evaluate health care outcomes. Medical records research is usually institution or practice specific; therefore, the number of patients is much smaller than those seen in larger insurance-based claims databases. Although smaller in scope, medical records research often allows for greater variety in the type of clinical data that is available compared with insurance and institutional claims data. Medical record data include laboratory values, diagnostic reports, and other aspects of care that would not be captured with billing codes in insurance claims data.

Over the past 10 years, there has been significant investment from the Office of the National Coordinator (ONC) to link EMRs across health care practices and institutions to create health information exchanges (HIE). Although HIEs are primarily developed to improve information sharing for the purpose of patient care and organizational efficiency, they represent a rich data source for researchers. Additional information related to medical records research can be found in feature on pediatric medical records research.

National Surveys and Disease Registries

National surveys and disease registries are retrospective databases that are publically accessible and de-identified, allowing access and eliminating the need for permission security concerns because of the protected health information (PHI). The U.S. government funds many national surveys that regularly collect detailed information about disease and health care utilization. Surveys such as NAMCS and MEPS (an AHRQ survey) are designed to be nationally representative samples, which allows for extrapolation from relatively small samples to national estimates. Additionally, these surveys are typically conducted annually, which enables researchers to study population health trends longitudinally over multiple years.

Disease registries aggregate detailed information about incident cases and the care received for a specific disease. Disease registries such as the Surveillance, Epidemiology, and End Results (SEER) program track data on specific diseases and can be useful for explaining national disease burden and treatment patterns. The SEER program, for instance, has been tracking cancer cases since 1973. Registries, either federally or privately funded, can be powerful tools for examining treatment patterns and disease burden over time. Patient-specific disease registry data can often be linked to health insurance claims data to provide a more comprehensive picture of the health care services used by a registry patient. Pediatric-specific surveys and disease registries will be discussed in the following.

Advantages of Database Research

There are a number of advantages in using large health care databases, including the availability of an abundance of data representing real world patient interactions with the health care system, the relatively low cost of collecting the data, and the relative ease of obtaining the data. When compared with randomized clinical trials, there is an exponential magnitude increase in the number of subjects available to the researcher. For example, RCTs studying the safety and effectiveness of a drug product may include 500 to 5000 patients, whereas a large database study may be able to amass a cohort of hundreds of thousands of real-world patients taking this same medication. In addition, most claims databases have multiple years' worth of data as compared with RCTs. The longitudinal nature of data collection allows the researchers to examine the outcome of interest over a longer time period as compared with RCTs. The costs associated with RCTs can limit the scope of the research project, both in the size and the variability of the study population. Another important offering with claims database research is the "real world" applicability. Most RCT study protocols have tight inclusion criteria which limits the generalizability of the study to the broader patient population. Also, RCTs are subject to an unintended Hawthorne effect, where subjects behave differently because they are being watched, which may impact the outcome of interest. Claims databases contain health care utilization data, including all the imperfections of non-compliance and comorbidities; this may provide a more accurate reflection of outcomes than do RCTs.

A major advantage of using large databases for research is the ability to link data. During RCT, data collection is often manual, limited in scope, and often associated with the outcome of interest. Database research, in contrast, allows the researcher to ascertain a large variety and number of data elements electronically. Although the outcome of interest or association may be similar to that of a RCT, database linking offers an advantage of evaluating a much larger sample size and explore associations beyond what a RCT can provide. In addition, database linkages can be performed to augment

limited information available in the primary research database. For example, U.S. Census data are often linked to insurance claims data to account for the demography and health of a patient's community at the ZIP Code or county level.

Disadvantages of Database Research

With the exception of the national surveys, most databases were created for non-research purposes. For example, claims databases were created to facilitate payments, and medical records are meant to aid in the care of individual patients. Although the databases can be quite extensive with regard to the number of patients and the data available, it can be challenging to implement a true experimental design that directly measures the effect of an intervention on the outcome of interest. Unlike an RCT that allows you to randomize subjects and control for selection bias and known and unknown confounding variables in the study design, database research studies require a more thoughtful approach to minimize these biases in either the design or analyses. Confounding variables are one of the biggest challenges in database research, making it difficult to distinguish the association between the outcome of interest and independent factors that may or may not have attributed to that outcome. A more detailed discussion of confounding and ways to mitigate its impact is presented in the following.

The amount of information provided in claims databases can be restricted, limited in scope, or entered incorrectly. Although the data available is much greater than in RCTs, the variety of data available is limited, and the database researcher has limited control over what variables are recorded. For example, clinical data such as laboratory values are often absent in insurance claims databases. In addition, information that is entered into the database may be entered incorrectly. An office visit may have multiple ICD or CPT codes associated with it based upon the diagnosis and procedures conducted during that episode of care. The coding of these procedures may be done incorrectly, whether from the provider documentation or a coding error by the office biller. Another factor that may influence the correct ICD or CPT code may be reimbursement rate for that respective code. For example, when faced with two codes describing the same episode of care, the physician/biller may choose the code with the higher reimbursement rate ("upcode"). Inversely, an insurance company may use "downcoding" to pay for the least expensive intervention.

Finally, a disadvantage of using claims data are the inability to capture resources that are consumed but a claim is not submitted. Over-the-counter medications are often purchased by a patient, but no claim is submitted because an insurer will not cover this class of drugs. Prescription claims data are also unable to capture when a patient pays cash for a prescription medication. Research studies examining the impact of over-the-counter medications or lower cost generic drugs may be faced with an under-represented sample of

medication use in the claims database as compared with that consumed in the real world. For example, a study looking at proton pump inhibitors use may underestimate how many patients are taking these drugs if it only used prescription claims data because of their OTC availability.

DATABASE RESEARCH STUDY CONSIDERATIONS

Preparing to Conduct Database Research

Identification of the research question is the most important step for any type of research. This is especially important in database research, because defining the intended question can help identify which data source one should use along with the appropriate study design. Identifying the target databases to answer the research question may be challenging. Most large databases are either proprietary or require organizational membership to access the information. Institutions that participate in registries are expected to contribute their own data and have appropriate quality assurance measures in place to validate the accuracy and reliability of the data through auditing mechanisms.

As researchers begin to identify the research question, it is important to use the literature to assist in study design. For example, database research protocols often use an algorithm of subject selection for outcomes analysis (e.g., selection of a specific ICD or CPT code). However, there may be unexpected variability with the selected code(s) that may impact the results of the study. The review of published studies/meta-analysis will assist the researcher in ensuring appropriate coding algorithms are in place to capture the true outcome of interest. For example, are multiple codes used in the algorithm to identify cases or the outcome of interest? If multiple codes are used, can the algorithm validate each one or the group of codes together? Thoughtful consideration and review of the research question coupled with the appropriate database inquiry can result in a wealth of information for the researcher to use.

Confounding Variables

Most databases contain observational data that has been collected as a result of routine clinical practice in the real world: the investigator did not assign the treatments or exposures being evaluated. In contrast, a randomized trial evenly distributes confounding factors between the treatment and control groups, allowing both known and unknown or unmeasured confounders between the groups being studied. Any difference in outcome that remains between the comparison groups would be attributed to the impact of the treatments, assuming other threats to the internal validity of the study do not exist.

Treatments are not randomly assigned in "real life" databases and thus, it is likely that a person's likelihood of receiving a certain medication therapy and experiencing a

health outcome are the product of other patient-, provider-, or system-level characteristics. These factors are referred to as *confounders* and must be addressed in either the study design or analysis to avoid biased results. As described earlier, a confounder is a third variable that is independently associated with both the exposure and treatment being studied as well as the outcome of interest. For example, if an investigator wanted to compare the impact of β -blockers with that of angiotensin-converting-enzyme (ACE) inhibitors on an outcome like mortality using a large database, there likely are many measurable factors that confound the observed relationship between the selection of a lipid-lowering drug agent and patient mortality. Prescribers may be more likely to use β -blockers in older patients and in those with previous cardiovascular disease, whereas ACE inhibitors may be prescribed more often to patients with diabetes. In this case, the variables representing previous cardiovascular disease, age, and diabetes are associated with the treatments and all three of the variables are recognized risk factors for death—that is, these variables could confound the results of the study. A pediatric-specific example is the use of insurance claims data to examine the effects of antidepressant adherence on adolescent suicide. Failing to control for a subject's family history of depression may bias the estimated effect of the study exposure on the study outcomes, because a family history of depression may be independently associated with how adherent the subject is to therapy as well as the likelihood to commit suicide.

There are several ways to mitigate the bias that results from confounding variables. The first is the use of inclusion/

exclusion criteria to select a study cohort less vulnerable to the effects of confounding. Another tool to control for confounders in regression modeling, assuming the database allows one to reliably measure the confounder. Regression analysis is not a panacea: residual confounding may remain even after including the measured confounding variables, and regression cannot account for unmeasured or unknown confounders. Finally, a popular approach is to use propensity scores to match subjects that experience the study outcomes with those that do not experience the study outcome based on very similar exposures. Confounding is a significant challenge to all observational study designs, including case control and cohort studies.

Common Study Designs

Cohort (retrospective and prospective), cross sectional, and case control are the most common observational study types. A summary of the different types of observational studies used in database research is presented in Table 3-1.

Cohort Studies

Cohort studies may be retrospective or prospective in nature. In both cases, groups are identified based on the presence or absence of a treatment or exposure. In a retrospective cohort study, the outcome of interest has already occurred at the time the investigator initiated the study. This is a common design used with database research because the investigator does not have to wait—in some cases many years—for an outcome to occur. The availability of years of data allows investigators

Table 3-1. Observational Study Overview

Study Type	Description	Weaknesses	Reducing Bias Strategies
Cohort studies • Retrospective • Prospective	- Produces the most reliable results in observational studies - Able to establish direction and magnitude of causal relationship - Allows to calculate incidence rates, relative risks - Able to examine changes within and between individuals - Allows for the examination of multiple outcomes of the same exposure	- Expense - Inefficient for rare diseases - Lost to follow-up - Conditions might be altered between pre and post-test	- Matching - Pairing - Stratification - Repeated measurements
Cross-sectional studies	- Data collected at one specific time point - Can study several exposure factors and outcomes simultaneously - Inexpensive (e.g., survey)	- Does not determine causality - Not appropriate if either exposure or outcome is rare	Random sampling
Case control studies	- Subjects selected based on whether disease present or absent - Best for rare diseases - Examines multiple exposures to a single disease	- Susceptible to selection and recall bias - Selecting controls can be difficult - Cannot estimate prevalence/incidence	- Matching - Pairing - Stratification

to go back into historical records to assign groups based on an exposure or treatment. For example, investigators could use an insurance database to identify patients that received a new prescription for a beta-blocker or ACE inhibitors 20 years ago. Investigators can use the same database to determine whether the outcome of interest has occurred in the subsequent 20 years, making the study significantly shorter and cheaper to conduct. A disadvantage of this design is that the investigator is limited to the data already recorded in the database. Missing and/or ambiguous data become a limitation of the study. Alternatively, investigators using a prospective cohort design may have the opportunity to contact the study participants and collect additional data or clarify data found in the study database. Cohort studies in very large databases are particularly useful for the evaluation of a rare exposure. Finally, cohort studies allow the evaluation of multiple outcomes in the same study.

Cross-sectional Studies

Cross-sectional studies are generally associated with surveys in which exposures and outcomes are gathered at the same point in time. Because exposure (treatment) and outcome are assessed at the same time, cross-sectional studies cannot distinguish whether the exposure (treatment) preceded the outcome or whether the outcome influenced the subsequent exposure (treatment). Thus, cross-sectional studies are useful for measuring the prevalence of disease or treatment and for the generation of hypotheses that can be confirmed or rejected using other study designs, but are not generally suitable for hypothesis testing.

Case Control Studies

In a case control study, patients are assigned to a study group based on the presence (case) or absence (control) of the outcome of interest. Investigators then look backwards in time from the outcome event to assess exposure status for each subject. Investigators may match multiple controls to each case to improve statistical power. Because study subjects are selected based on the presence or absence of outcome, incidence cannot be calculated. Instead, the odds ratio replaces the relative risk as the appropriate measure of association. The odds ratio always overestimates the relative risk. The degree of divergence between the odds ratio and relative risk depends upon the frequency of the outcome and the strength of the relationship between the exposure and outcome variables. When the outcome of interest is rare, the odds ratio is a good estimate of the relative risk. As the outcome becomes more common, the odds ratio begins to diverge from the relative risk.

Case control studies are less expensive to conduct than prospective cohort studies and randomized trials. Study duration is shorter because no follow-up time waiting for the outcome to develop is needed. These studies are always retrospective in nature because the outcome of interest has

already occurred. Selection bias is a significant challenge for investigators conducting case control studies. If the cases and controls are not drawn from the same population, the results are likely to be biased. Investigators may use several methodologic techniques to reduce the likelihood of selection bias. Matching a control to a case is one strategy commonly used. Investigators may also use a nested design in which the cases and controls are selected from a defined study cohort. Some studies will also use multiple control groups in the same study. When study results are similar for each of the control groups, the likelihood of selection bias is reduced.

EXAMPLES OF PEDIATRIC DATABASES

Medicaid Statistical Information System

The Medicaid and Statistical Information System (MSIS) is a large database used by the Centers for Medicare and Medicaid Service to review the eligibility, enrollment, program, utilization and expenditure data. The Medicaid information from each State and Territory is provided to the MSIS system, which includes the pediatric-specific Children's Health Insurance Program (CHIP) program. There are about 8.4 million children enrolled in CHIP and the database includes data related to health care research and evaluation activities, program utilization and expenditure forecasting. Further data analysis is available and can be found in the Medicaid Analytic eXtract (MAX) data warehouse. A large number of tutorials [are available online](#) to guide the researcher in data extraction and analysis. The MSIS system offers the advantage of an inexpensive, comprehensive database that contains a significant amount of CHIP information.

Pediatric Health Information System

The Pediatric Health Information System (PHIS) is a database sponsored by the Children's Hospital Association (CHA). The 43 stand-alone pediatric hospitals within the United States contribute data that include clinical and resource utilization measures for inpatient, outpatient surgery, ED, and observation encounters. Institutions can compare ICD codes, billing transactions, resource utilization and other information to guide clinical care development. For example, PHIS data can identify practice patterns with associated outcomes. Although one must be a member of CHA to participate in the database, the standing reports and ability to create custom reports provides an excellent source of data for those wishing to conduct pediatric database research. An example of a research study using PHIS data is reviewed in the Clinical and Practice Updates module.

The Extracorporeal Life Support Organization

The Extracorporeal Life Support Organization (ELSO) is an international consortium of health care centers and practitioners (e.g., physicians, nurses, pharmacists, perfusionists,

respiratory therapists, researchers) who focus on the development, evaluation, and improvement of extracorporeal membrane oxygenation (ECMO) therapies. In addition to ECMO, this organization evaluates innovative therapies for multi-organ failure in pediatric patients. Since 1998 ELSO has compiled a database of ECMO treatment strategies and outcomes. Each center is responsible for entering standardized data elements (including outcomes) specific to their institution.

The Resuscitation Outcomes Consortium

The Resuscitation Outcomes Consortium (ROC) comprises database and infrastructure support to research the outcomes associated with cardiopulmonary arrest and severe traumatic injury. Because the volumes of such events are limited within an individual health care organization, the goal is to pool data for review to establish evidenced-based best practices. For a large part, data collection focus is on pre-hospital and early hospitalization because of the critical importance of this time frame.

The Vermont Oxford Network

The Vermont Oxford Network (VON) is a multidisciplinary consortium that is focused on the health care of premature and term infants. Established in 1988, the Group represents more than 1000 Level I and II health care centers around the world. The primary focus of the VON is to collect and analyze clinical and operational data that improve care in premature and term neonates. The database contains over 2 million patients representing more than 63 million patient days. In this comprehensive neonatal database, institution-specific outcomes can be benchmarked against comparable units or compared across the entire database. A significant number of studies have been published from the group, which requires considerable data collection and entry for inclusion in the database. Regardless, the VON database can be used to determine the effectiveness of treatment modalities and the creation of evidence-based guidelines.

The National Survey of Children's Health

The National Survey of Children's Health is a collaborative effort between the Maternal and Child Health Bureau at the Health Resources and Services Administration, the National Center for Health Statistics at the CDC, Child and Adolescent Health Measurement Initiative, and the National Technical Expert Panel. The purpose of the surveillance database is to examine the physical and emotional health of children throughout all 50 states. Initiated in 2003, the survey of about 100,000 children examines factors related to the well-being of children including medical, home, family interactions, parental health, schools experiences, and safe neighborhoods. Data collection is centered at the CDC and represents the overall well-being of non-institutionalized children throughout the United States.

Canadian Pharmacogenomics for Drug Safety

The large Canadian Pharmacogenomics for Drug Safety database identifies and collects biologic samples from children and adults who take medications and have adverse drug reactions; this is compared with children and adults who take the same medications and do not experience any adverse drug effects. The goal of the registry is to determine if genetic differences between the two groups contribute to incidence of adverse drug reactions. The researchers intend to develop patient-specific drug dosing guidelines to prevent future adverse drug reactions. Although not a claims database, the Canadian consortium gathers a significant amount of data that can be used to correlate factors associated with adverse drug events in both pediatric and adult patients. The collection of information throughout Canada provides a unique database that is independent of insurance claims data. Although a similar program does not currently exist in the United States, it is anticipated that the evolution of Precision Medicine programs will result in a similar type of database.

CONCLUSION

There are considerable opportunities for pediatric database research. As health care providers seek to optimize treatment plans in pediatrics, the access to large databases that examine outcomes in "real world" settings is extremely important. It is important that the investigator have a strong understanding of pediatric pathophysiology and pharmacotherapy to optimize the design of the research algorithms.

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Self-Assessment Questions

Questions 41–43 pertain to the following case.

Z.T. is a researcher interested in examining health disparities of children in the 30 most populous cities throughout the United States. Specifically, she would like to examine the impact of the Affordable Care Act on health care coverage of children less than 12 years of age. Z.T. will use information from three large national insurance companies.

41. Which one of the following is the most appropriate data source for Z.T. to consider?
 - A. Medical claims database
 - B. Provider claims database
 - C. Enrollment files database
 - D. Prescription claims database
42. Z.T. intends to examine the rates of hospital admission caused by asthma exacerbations in the same pediatric patient population. Specifically, she is interested in determining if the change in health care insurance resulted in a change in ED visits. Which of the following data sources would be best for Z.T. to consider?
 - A. Medical claims databases linked with enrollment files databases
 - B. Provider claims database linked with medical claims databases
 - C. Enrollment files database linked with provider claims databases
 - D. Prescription claims database linked with provider claims databases
43. Z.T. is asked by a student to describe the type of study design. Which one of the following is the best response for Z.T. to give the student?
 - A. Retrospective cohort study
 - B. Cross sectional study
 - C. Demographic study
 - D. Case control study
44. A state drug utilization review board is interested in examining their state Medicaid database to examine adolescent consumption of antihistamines. Specifically, the U.S. Department of Health and Human Services is concerned about the allergens that may be affecting the rural state and health outcome related to poor air quality. Which one of the following is the most appropriate consideration for the state drug utilization review board ?
 - A. The state Medicaid database should capture all the relevant information.
 - B. The state Medicaid database does not include adolescent patients because they are not considered children and would not be included.

- C. The state Medicaid database will not capture antihistamines that are consumed OTC and possibly under-represent true consumption.
- D. The state Medicaid database does not use “real-time” data because of data uploads and thus, may not be up to date.

Questions 45 and 46 pertain to the following case.

The CEO of the KinderHome Pediatric Hospital has concerns related to the expansion of floor-based pharmacy services. Although there is sufficient literature supporting pharmacist participation in multidisciplinary rounds, she is concerned that the economic model does not warrant sustainability. She would like to survey and research pharmacist staffing ratios in other pediatric hospitals and study the impact that these floor-based pharmacists have on medication errors, adverse drug events, and length of stay.

45. Which one of the following databases would best assist the KinderHome CEO in deciding the proposed expansion?
 - A. Hospital medical claims
 - B. Pediatric health information systems
 - C. Medicaid Statistical Information System
 - D. Prescription claims
46. Preliminary data reveal that pharmacists located in the neonatal ICU have been shown to decrease medication errors and length of stay. The KinderHome CEO wishes to examine, in more detail, the impact that pharmacists have in improving outcomes in the neonatal ICU. Which one of the following would be the best to investigate such information (assuming that the hospital has a membership for that respective organization)?
 - A. Vermont Oxford Group
 - B. The National Survey for Children’s Health
 - C. The Resuscitation Outcomes Consortium
 - D. The Extracorporeal Life Support Organization
47. An algorithm is created within a research protocol to identify CPT codes created by inpatient pharmacists to evaluate the outcome of interest (drug induced renal toxicity) and the pharmacist’s role in reducing aminoglycoside-associated renal toxicity. The researcher has identified multiple CPT codes in the algorithm to collect the various forms of renal toxicity that may be associated with medication orders (e.g., interstitial nephritis, acute tubular necrosis). Which one of the following would be the best next step for the research team?
 - A. Because CPT codes are not generated by inpatient pharmacies, the study has to be redesigned.
 - B. Conduct a pilot study with the research algorithm to examine its ability to capture the outcome of interest.

- C. Review the decision support tool within the computerized physician order entry system at the respective institution(s) to capture patients who developed aminoglycoside-associated renal toxicity.
- D. Use a prescription claims database to identify patients who would have received aminoglycosides.

Questions 48–51 pertain to the following case.

In 2001, the American Academy of Pediatrics published “AD/HD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents.” The CALMED research team wishes to compare the treatment strategies of AD/HD following publication of these guidelines. Specifically, the CALMED team wishes to evaluate the drug prescribing patterns before and after the guideline publication within a large insurance company that covers 1.2 million patients throughout the United States.

48. Which would be the most appropriate database for the CALMED team to begin examining?
 - A. Inpatient pharmacy medical records
 - B. Pediatric health information system
 - C. The National Survey for Children’s Health
 - D. Prescription claims
49. The CALMED research team begins to analyze medication utilization patterns within the database. What is the most important data element required to capture the desired information?
 - A. Unique medication identifier
 - B. Medication name and manufacturer
 - C. ICD code for each medication
 - D. CPT code for each medication
50. The CALMED team is asked by the insurance company to review the possible association between cardiac arrhythmias and the use of methylphenidate. The insurance company wishes for the CALMED team to design a study using its database of 1.2 million patients. What would be the most appropriate study design to examine association between methylphenidate and cardiac arrhythmias?
 - A. Demographic study design
 - B. Case control study design
 - C. Randomized, controlled study design
 - D. Retrospective cohort study design
51. The CALMED research team discovers a possible association between the development of tachyarrhythmia in Asian adolescent females who were prescribed methylphenidate. The researchers would like to explore the possibility of polymorphisms contributing to this adverse

event. Which one of the following would be the best database to further explore this possible association?

- A. Pediatric Health Information System database
 - B. Canadian Pharmacogenomic for Drug Safety database
 - C. United Health care medical claims database
 - D. Medicaid Statistical Information System
52. A research team wishes to examine the health care utilization patterns of children with otitis media who live at or below the poverty line. In particular, they wish to compare the use of antibiotics and placement of tympanostomy tubes in children who live in states in the Northeastern United States versus children who live in Southwestern states. Which one of the following would be the best database for the team to use?
 - A. Medicaid Statistical Information System
 - B. The National Survey for Children’s Health
 - C. The Resuscitation Outcomes Consortium
 - D. Pediatric Health Information System database
 53. A pediatric infectious disease research team is interested in conducting a survey of family practice physicians and pediatricians within a five-state region to determine the prevalence of pediatric osteomyelitis and the treatment strategies used by these physicians. Which one of the following would be the best design for this study?
 - A. Prospective cohort
 - B. Cross-sectional
 - C. Retrospective cohort
 - D. Case control

Questions 54–58 pertain to the following case.

K.G. is a PGY2 pediatric resident who is in the process of determining his residency research project. Based upon observations during his PGY1 general residency, K.G. is very interested in working with the hospital’s information technology department to evaluate data within the Pediatric Health Information System. In particular, he is very interest in neonatal hypertension.

54. K.G. meets with the preceptor regarding the appropriateness of this study. Which one of the following is the best response for the preceptor to give K.G.?
 - A. This is the wrong database; you should be using the Resuscitation Outcomes Consortium database.
 - B. This is the correct database, but you will need to properly define the research question.
 - C. This is the correct database, but you should consider linking that data with the Medicaid Statistical Information System.
 - D. This is the wrong database; you should be using Medicaid Statistical Information System.

55. K.G. determines that his research question will examine dopamine, dobutamine, epinephrine, hydrocortisone, and norepinephrine use in 43 CHCA NICUs from 2005-2015. Which one of the following best describes K.G.'s study design?
- Prospective cohort
 - Cross-sectional
 - Retrospective cohort
 - Case control
56. Which one of the following is the best method for K.G. to identify patients within the NICU that had hypotension?
- ICD codes for hypotension
 - CPT codes for hypotension
 - Medical records within each institution
 - Prescription claims identifier
57. K.G. wishes to examine hypotension of prematurity and minimize confounding variables such as congenital heart disease, sepsis/meningitis, and patients who received extracorporeal membrane oxygenation. Which one of the following would be best way for K.G. to minimize confounding?
- Randomize patients equally among the congenital heart disease, sepsis/meningitis, and extracorporeal membrane oxygenation groups.
 - Exclude patients from the study if they have congenital heart disease, sepsis/meningitis, or received extracorporeal membrane oxygenation.
 - Create propensity scoring for each of the neonates that developed hypotension.
 - Identify matched controls to examine the impact of pharmacologic therapy on neonatal hypotension.
58. K.G.'s preceptor is intrigued by the study. Using the same database and same neonates K.G. identified, the preceptor wishes to examine the 5-year outcomes of the neonates who received dopamine, dobutamine, epinephrine, hydrocortisone, and norepinephrine between 2005 and 2010. In particular, the preceptor wishes to examine the rates of cerebral palsy in the neonates who received these agents. Which one of the following is the biggest challenge K.G.'s preceptor faces with this study?
- Conducting this study will be expensive.
 - The study may be subject to selection and recall bias.
 - Patients may be lost to follow-up.
 - The selection of matched controls will be difficult.
59. Which one of the following best exemplifies a benefit of using a disease registry as compared with an insurance claims database?
- Disease registries automatically link to insurance claims databases, so there would be no need to conduct research within an insurance claims database.
 - Disease registries can track diseases over time and insurance claims databases cannot.
 - All disease registries are funded by the United States government, so they are free with unlimited access to everyone.
 - Data are de-identified in a registry.
60. Which one of the following would best determine the incidence and relative risks of developing a perforation at the ileocecal valve with indomethacin therapy for patent ductus arteriosus?
- Retrospective cohort study
 - Case control study
 - Randomized, controlled clinical trial
 - Cross-sectional study

Learner Chapter Evaluation: Database Research.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

37. The content of the chapter met my educational needs.
38. The content of the chapter satisfied my expectations.
39. The author presented the chapter content effectively.
40. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
41. The content of the chapter was objective and balanced.
42. The content of the chapter is free of bias, promotion, and advertisement of commercial products.
43. The content of the chapter was useful to me.
44. The teaching and learning methods used in the chapter were effective.
45. The active learning methods used in the chapter were effective.
46. The learning assessment activities used in the chapter were effective.
47. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

48. Analyze the different types of database resources available for database research.
49. Evaluate the advantages and disadvantages of database research.
50. Estimate the impact that confounding has in the practice of database research.
51. Evaluate common study designs used in database research and assess their impact on interpretation of study results.
52. Design a plan that will assist the researcher in preparing to conduct pediatric database research.
53. Justify the use of popular pediatric databases and the information they contain for research.
54. Please provide any specific comments related to any perceptions of bias, promotion, or advertisement of commercial products.
55. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

Questions 56–58 apply to the entire learning module.

56. How long did it take you to read the instructional materials in this module?
57. How long did it take you to read and answer the assessment questions in this module?
58. Please provide any additional comments you may have regarding this module:

Clinical and Practice Updates I

Clinical and Practice Updates I Panel

Series Editors:

Marcia L. Buck, Pharm.D., BCPPS, FCCP, FPPAG

Clinical Coordinator
University of Virginia Children's Hospital
Professor
Department of Pediatrics
University of Virginia School of Medicine
Clinical Professor
Virginia Commonwealth University School of Pharmacy
Department of Pharmacy Services
University of Virginia Health System
Charlottesville, Virginia

Kalen B. Manasco, Pharm.D., BCPS

Clinical Associate Professor
Department of Clinical and Administrative Pharmacy
University of Georgia College of Pharmacy
Augusta, Georgia

Faculty Panel Chair:

Christopher Shaffer, Pharm.D., M.S., BCPS

Associate Dean
University of Nebraska Medical
Center College of Pharmacy
Assistant Professor
Department of Pharmacy Practice and Pediatrics
University of Nebraska Colleges of
Pharmacy and Medicine
Director, Pediatric Precision Medicine Program
Children's Hospital and Medical Center
University of Nebraska Medical Center
Omaha, Nebraska

Recorded Webcast: Pediatric Study Design

Author

Mary Jayne Kennedy, Pharm.D., DABCP

Professor and Chair
Department of Clinical Sciences
High Point University School of Pharmacy
High Point, North Carolina

Reviewers

Brian J. Cowles, Pharm.D.

Associate Professor and Vice Chair
Department of Pharmacy Practice
Albany College of Pharmacy and Health Sciences
Colchester, Vermont

Manal M. Abou Elkheir, Pharm.D., BCPPS, BCPS

Pediatric Clinical Pharmacist
Department of Pharmacy Services
King Saud University Medical City
Adjunct Clinical Assistant Professor
Department of Clinical Pharmacy
College of Pharmacy-King Saud University
Riyadh, Saudi Arabia

Interactive Case: Developing and Adopting Novel Therapies in the NICU

Author

Peter Gal, Pharm.D., FCCP, FASHP, FPPAG

Professor and Associate Dean for Academic Affairs
High Point University Fred Wilson School of Pharmacy
High Point, North Carolina

Reviewers

Brandy Zeller, Pharm.D., BCPPS

NICU Clinical Pharmacist
St. Louis Children's Hospital
St. Louis, Missouri

Kathleen Sprott, Pharm.D., BCPS, BCPPS

Clinical Specialist, Pediatrics/Solid Organ Transplant
Department of Pharmacy Services
Medical University of South Carolina
Adjunct Assistant Professor
Department of Clinical Pharmacy and Outcome Sciences
South Carolina College of Pharmacy
Charleston, South Carolina

Recorded Webcast: Medical Records Research

Author

Christopher Shaffer, Pharm.D., M.S., BCPS

Associate Dean
University of Nebraska Medical Center College of Pharmacy
Assistant Professor
Department of Pharmacy Practice and Pediatrics
University of Nebraska Colleges of
Pharmacy and Medicine
Director, Pediatric Precision Medicine Program
Children's Hospital and Medical Center
University of Nebraska Medical Center
Omaha, Nebraska

Reviewers

Melissa Gabriel, Pharm.D., BCPS

Medication Safety Manager
Pharmacy Department
Truman Medical Center
Kansas City, Missouri

Monica A. Puebla, Pharm.D., MBA, MHA, BCPS

Medication Error Prevention Specialist
Med-ERRS, Inc.
Horsham, Pennsylvania

The American College of Clinical Pharmacy and the authors thank the following individuals for their careful review of the Research and Study Design in Pediatrics I chapters:

Nicola G. Dahl, Pharm.D.

Medical Writer
Kanab, Utah

Ralph H. Raasch, Pharm.D., FCCP, BCPS

Associate Professor of Pharmacy (retired)
Division of Practice Advancement and Clinical Education
Eshelman School of Pharmacy
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

Consultancies: Mary Jayne Kennedy (NHLBI, Guilford Count Public Health); Donald Klepser (Viiv, Force Diagnostics); Melissa Ray (Pharmacist's Letter, Hospital Pharmacist's Letter)

Stock Ownership:

Royalties: Donald Klepser (NACDS)

Grants: Gary L. Cochran (USDHHS Office of the National Coordinator for HIT); Donald Klepser: (NACDS, Roche Diagnostics, ONC); Drew Roberts (Academy Health, NIH)

Honoraria:

Other:

Nothing to disclose: Manal M. Abou Elkheir; Margaret Burke; Brian J. Cowles; Melissa Gabriel; Peter Gal; Brent A. Hall; Anthony T. Podany; Monica A. Puebla; Emily L. Rowe; Mary Ryan; Christopher Shaffer; Kathleen Sprott; Courtney Sutton; Brandy Zeller

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Recorded Webcast: Pediatric Study Design

By Mary Jayne Kennedy, Pharm.D., DABCP

Reviewed by Brian J. Cowles, Pharm.D.; and Manal M. Abou Elkheir, Pharm.D., BCPPS

LEARNING OBJECTIVES

1. Demonstrate knowledge of the clinical research process, including the process for developing a study concept.
2. Analyze the most important elements in preparing a study protocol.
3. Identify the different types of study costs, and estimate these costs when preparing a budget.
4. Classify the various strategies used in recruitment and enrollment of pediatric subjects.

ABBREVIATIONS IN THIS CHAPTER

CRF	Case report form
DSMB	Data and Safety Monitoring Board
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional review board
SOP	Standard operating procedure

[*Table of other common abbreviations.*](#)

LINK TO RECORDED WEBCAST

- [Click here to begin this PedSAP activity.](#)
- [Click here to view a transcription of this recorded webcast.](#)

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- Basic principles of biostatistics
- Basic types of clinical trials
- Hypothesis creation and development
- Fundamentals of preparing a research study budget

[*Table of common pediatric laboratory reference values.*](#)

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- National Institute of Child Health and Human Development (NICHD). Clinical Trials and Clinical Research. <https://www.nichd.nih.gov/health/clinicalresearch/Pages/index.aspx>
- Food and Drug Administration. The Drug Development Process. Step 3: Clinical Research. www.fda.gov/ForPatients/Approvals/Drugs/ucm405622.htm

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Self-Assessment Questions

Questions 1–3 pertain to the following case.

Researcher T.J. is planning a clinical trial that will delve into an important pediatric pharmacy issue.

1. Which one of the following actions is most important to complete before T.J. can enroll the first patient?
 - A. Data analysis.
 - B. Database lock.
 - C. Study report preparation.
 - D. Independent review board (IRB) approval.
2. Which one of the following has the lowest likelihood of compromising the integrity of T.J.'s trial in human subjects?
 - A. Value of the scientific question
 - B. Balance of risks and benefits
 - C. Subject selection based on locality
 - D. Independent review by IRB
3. Which one of the following aspects of the study would be most feasible to determine after T.J. initiates the clinical trial?
 - A. Number of patients needed to evaluate protocol sample size
 - B. Eligibility criteria
 - C. Study design
 - D. Degree to which the trial outcomes are met
4. During which one of the following steps in the clinical research process is it best to include initiation of the study timeline?
 - A. Developing the concept
 - B. Preparing the protocol
 - C. Protecting participants
 - D. Conducting and monitoring the study
5. You are developing a plan to study the efficacy of a new antihypertensive agent in children ages 6–12 years. Which one of the following would be most important to incorporate into the protocol to ensure the accuracy of data collected?
 - A. Adequate sample size
 - B. Age-appropriate blood pressure cuffs
 - C. Ethnic diversity
 - D. Sex diversity
6. Which one of the following is best to consider in estimating the sample size for a pediatric clinical study?
 - A. Availability of age-appropriate reference ranges
 - B. Knowledge of the adverse effect profile
 - C. Availability of age-appropriate measurement devices
 - D. Knowledge of the difference you want to detect
7. Which one of the following best exemplifies an indirect study cost?
 - A. Personnel
 - B. Subject reimbursement
 - C. Institutional overhead
 - D. Consumable supplies
8. Which one of the following best exemplifies a responsibility of the Data Safety Monitoring Board?
 - A. Ensuring subject privacy
 - B. Ensuring subject confidentiality
 - C. Ensuring validity of analytical assays
 - D. Making recommendations regarding study continuation
9. Which one of the following steps in the clinical research process is most likely to include preparation of a study report?
 - A. Study closure
 - B. Developing the study concept
 - C. Conducting and monitoring the study
 - D. Data analysis and interpretation
10. You are a researcher conducting a trial of a new antibiotic in neonates. The last subject has just completed all required study procedures, and all study sites have been closed. Which one of the following would be the most appropriate next step?
 - A. Perform an interim data analysis.
 - B. Submit data to the Data Safety and Monitoring Board for review.
 - C. Check data for completeness and reconcile as needed.
 - D. Lock the study database.

Learner Chapter Evaluation: Recorded Webcast: Study Design.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
 - Agree
 - Neutral
 - Disagree
 - Strongly disagree
1. The content of the chapter met my educational needs.
 2. The content of the chapter satisfied my expectations.
 3. The author presented the chapter content effectively.
 4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
 5. The content of the chapter was objective and balanced.
 6. The content of the chapter is free of bias, promotion, and advertisement of commercial products.
 7. The content of the chapter was useful to me.
 8. The teaching and learning methods used in the chapter were effective.
 9. The active learning methods used in the chapter were effective.
 10. The learning assessment activities used in the chapter were effective.
 11. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

12. Demonstrate knowledge of the clinical research process, including the process for developing a study concept.
13. Analyze the most important elements in preparing a study protocol.
14. Identify the different types of study costs, and estimate these costs when preparing a budget.
15. Classify the various strategies used in recruitment and enrollment of pediatric subjects.
16. Please provide any specific comments related to any perceptions of bias, promotion, or advertisement of commercial products.
17. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

Interactive Case: Developing and Adopting Novel Therapies in the NICU

By Peter Gal, Pharm.D., FCCP, FASHP, FPPAG

Reviewed by Brandy Zeller, Pharm.D., BCPPS; and Kathleen Sprott, Pharm.D., BCPS, BCPPS

LEARNING OBJECTIVES

1. Demonstrate an understanding of clinical practice guidelines and their intent.
2. Account for the frequency with which practice guidelines and expert opinions are reversed in medical practice and the areas of vulnerability for neonatal practice guidelines.
3. Evaluate when early adoption of new therapeutic practices may be indicated.
4. Argue the potential negative impact of early adoption of expert panel practice guidelines founded primarily on systematic reviews of studies with several limitations, without sufficient consideration for future outcomes.
5. Account for the inherent flaws of many expert guidelines and recommendations, and place in perspective the pharmacologic considerations for when guidelines and dosing handbooks may be ill informed.

ABBREVIATIONS IN THIS CHAPTER

AAP	American Academy of Pediatrics
BPD	Bronchopulmonary dysplasia
NEC	Necrotizing enterocolitis
NICU	Neonatal ICU
ROP	Retinopathy of prematurity
TDM	Therapeutic drug monitoring
VON	Vermont Oxford Network

[Table of other common abbreviations.](#)

LINK TO INTERACTIVE CASE

- [Click here to begin this PedSAP activity.](#)

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- Common neonatal diseases and their usual therapies
- Commonly used handbooks with recommended drug doses for neonates
- Basic issues involved in proper literature critique
- Important considerations about how study design affects results

[Table of common pediatric laboratory reference values.](#)

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Self-Assessment Questions

11. You wish to implement a new gentamicin dosing strategy involving a 7-mg/kg loading dose and post-load concentrations at 2 and 12 hours to calculate individual maintenance dosing. Which one of the following justifications best supports implementation of this new strategy?
 - A. Pharmacokinetic and pharmacodynamic principles
 - B. Clinical research showing poor clinical outcomes with current dosing
 - C. Statistical flaws in current studies obscuring therapeutic benefits
 - D. Newly introduced guidelines supporting the 7-mg/kg loading dose
12. Your neonatal ICU (NICU) is having a problem with high rates of retinopathy of neuropathy (ROP) compared with others in the Vermont Oxford Network (VON). Because ROP is often associated with high levels of oxygen use, you suggest a lower oxygen use strategy in which Sao_2 values are maintained at 75%–85% instead of over 90%, as is usual practice. The team likes the idea but wants to be sure it is safe and effective. Which one of the following study designs best helps overcome the greatest difficulty in addressing comparative safety and/or efficacy between the two Sao_2 values?
 - A. Treat all neonates with lower oxygen, and compare ROP rates with rates before the change.
 - B. Randomly assign infants 24–27 weeks' gestation to low oxygen, and compare ROP rates with infants 28–32 weeks' gestation receiving higher oxygen.
 - C. Change all infants to low oxygen, and compare ROP rates with VON for that year.
 - D. Create age- and sex-matched infant pairs, treat half with low oxygen and half with high oxygen, and compare ROP rates.
13. You want to begin using acetaminophen as first-line treatment for patent ductus arteriosus (PDA) closure because you have not been very successful with ibuprofen at standard doses of 10 mg/kg/day for 3 days (40% closure). You have available standard acetaminophen dosing guidelines of 5–10 mg/kg/day for this treatment, and you are considering comparing the closure rates with ibuprofen closure rates in the past 2 years. The team agrees to this approach. Which one of the following is most likely to produce a problem with either conducting the study or interpreting study results?
 - A. Acetaminophen is known to be inferior to ibuprofen, so patients should not be subjected to an inferior drug.
 - B. You have not ensured optimal dosing of either drug to make a fair comparison of their efficacy.
 - C. Use of acetaminophen in your NICU has better PDA closure rates than other NICU PDA closure rates reported in VON (a program you participate in).
 - D. A control group not treated with any drug should be included to get a proper sense of acetaminophen efficacy.
14. Which one of the following statements best justifies the use of clinical guidelines in the NICU?
 - A. They consistently offer the best analysis of the literature.
 - B. They tend to remain constant, so practices do not have to change.
 - C. They reduce the variability of approaches within a practice.
 - D. They ensure that neonatologists cannot be sued.
15. Which one of the following study designs is best to monitor quality improvement in outcomes within a NICU as a result of early adoption of a new treatment in a clinical practice?
 - A. Meta-analysis.
 - B. Systematic review.
 - C. Sequential analysis.
 - D. Controlled clinical trial.
16. A new AAP guideline recommends ampicillin and cefotaxime as first-line treatment for early-onset sepsis in neonates weighing less than 1000 g. The authors acknowledge the risk of increased antibiotic resistance and the associated higher mortality with cefotaxime, but they state their concern for more *Escherichia coli* meningitis in this population and fear of possible gentamicin nephrotoxicity. Which one of the following strategies would be best to implement in a NICU wishing to challenge these guidelines?
 - A. Continually implement guidelines because they are always correct.
 - B. Compare your *E. coli* sepsis, meningitis, and mortality with others in the VON, and only change to the other guidelines if your rates are higher than average.
 - C. Calculate the cost difference for gentamicin versus cefotaxime, and use the additional costs as a basis for avoiding the new guidelines.
 - D. Do a retrospective chart review for several years to assess previous annual rates of *E. coli* meningitis, *E. coli* infection, and clinical outcomes with standard ampicillin plus gentamicin treatment, and evaluate whether any changes in these rates over the several-year study are observed.

17. A new study that uses practice-based data in VON showed a decrease in mortality when Infasurf was used for respiratory distress syndrome (RDS) versus Survanta. This large study included more than 5000 patients. In addition, statistical analysis showed it had the greatest impact when used in newborns below 1000 g and had a number needed to treat (NNT) of 8 compared with Survanta for preventing RDS. An editorial states these results as a compelling reason to convert all NICUs to exclusive Infasurf use. Which one of the following statements best interprets these data?
 - A. These are compelling data to become an early adopter of Infasurf use because it is certainly beneficial.
 - B. This type of research, using routinely collected data, is inaccurate; thus, it should be ignored.
 - C. The NNT of 8 is insufficient to change clinical practice. Data are only compelling when the NNT is below 5.
 - D. Routinely collected data tend to overestimate benefits; thus, the data are interesting but not compelling for change.
18. You are using theophylline as a bronchodilator and respiratory stimulant in preterm infants because of a caffeine shortage. The drug seems to be working well with no clinical signs of toxicity. A random theophylline concentration collected by the nurse practitioner comes back at 15 mcg/mL; consequently, she wants to lower the theophylline dose to target a concentration of 6 mcg/mL because the FDA guidelines recommend 6–10 mcg/mL as therapeutic. Which one of the following is the most reasonable response to this colleague?
 - A. If the FDA recommended it, you should adhere to that target concentration.
 - B. Because the nurse practitioner prefers that target, the dose should be adjusted to achieve 6 mcg/mL.
 - C. The FDA target theophylline concentrations of 6–10 mcg/mL will likely result in excessive therapeutic failures, so the dose should be unchanged.
 - D. The dose should be held until the theophylline concentration falls below 6 mcg/mL and then reinitiated at a lower dose.
19. Treatment of seizures in newborns continues to be primarily with phenobarbital or phenytoin because of extensive clinical experience with their use and dosing. However, both drugs are known to promote neuron death in the hippocampus and may thus place newborns at risk of long-term neurodevelopmental and psychiatric disorders. Given the availability of other antiepileptic drugs like levetiracetam that do not cause neuronal cell death and that, in fact, may be neuroprotective, which one of the following is most reasonable regarding the continued use of phenobarbital or phenytoin?
 - A. The extensive published experiential case series with these drugs makes them better than a relatively new option like levetiracetam.
 - B. Although clinical trials comparing levetiracetam and phenobarbital show equal efficacy but better safety with levetiracetam, the trials are small, and only a trial involving thousands of patients should change long-standing clinical practice.
 - C. Even though phenobarbital causes known long-term neurotoxicity in newborns treated for seizures, the unknown toxicity risks from levetiracetam may be greater.
 - D. Given the known long-term neurotoxicity of phenobarbital and phenytoin and the limited controlled clinical trials with these agents, only practice habit can explain their ongoing use as first-line antiepileptic drugs.
20. Which one of the following is the most reasonable approach to early adoption of new therapies?
 - A. Any new double-blind controlled clinical trial results are sufficient basis for early adoption into clinical practice.
 - B. Clinical trial results should be consistent with physiologic and pharmacologic expectations before they are considered for early adoption.
 - C. Early adoption of a new clinical practice should only be tried by recognized experts, and when they deem a new practice ready, it should be rapidly adopted.
 - D. Early adoption of a clinical practice should only be considered after multicenter clinical trials confirm its value.

Learner Chapter Evaluation: Interactive Case: Novel Therapies in the NICU.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

18. The content of the chapter met my educational needs.
19. The content of the chapter satisfied my expectations.
20. The author presented the chapter content effectively.
21. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
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Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

29. Demonstrate an understanding of clinical practice guidelines and their intent.
30. Account for the frequency with which practice guidelines and expert opinions are reversed in medical practice and the areas of vulnerability for neonatal practice guidelines.
31. Evaluate when early adoption of new therapeutic practices may be indicated.
32. Argue the potential negative impact of early adoption of expert panel practice guidelines founded primarily on systematic reviews of studies with several limitations, without sufficient consideration for future outcomes.
33. Account for the inherent flaws of many expert guidelines and recommendations, and place in perspective the pharmacologic considerations for when guidelines and dosing handbooks may be ill informed.
34. Please provide any specific comments related to any perceptions of bias, promotion, or advertisement of commercial products.
35. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

Recorded Webcast: Medical Records Research

By Christopher Shaffer, Pharm.D., M.S., BCPS

Reviewed by Melissa Gabriel, Pharm.D., BCPS; and Monica A. Puebla, Pharm.D., MBA, MHA, BCPS

LEARNING OBJECTIVES

1. Classify the elements and functions of the medical record.
2. Apply real-world data to clinical research methods.
3. Analyze the strengths and weaknesses associated with medical records research.
4. Assess examples of pediatric-specific medical records research.

ABBREVIATIONS IN THIS CHAPTER

BCMA	Barcode medication administration
CPOE	Computerized physician order entry
EHR	Electronic health record
EMR	Electronic medical record
HIPAA	Health Insurance Portability and Accountability Act
ICD	International Classification of Diseases
IRB	Institutional review board
IT	Information technology
PHIS	Pediatric Health Information System
PHR	Patient health record

[*Table of other common abbreviations.*](#)

LINK TO RECORDED WEBCAST

Topic Article

- [Moffett BS, Humlicek TJ, Rossanno JW, et al. Readmissions for heart failures in children. J Pediatr 2016;177:2113-7.](#)

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Practice Points

- Paper and electronic medical records (EMRs) contain considerable clinical and administrative data that can be used for research purposes.
- The transition from paper medical records to EMRs has allowed for expansive medical records research opportunities.
- EMRs contain functionality in results management, orders management, decision support, electronic communication, patient support, and administrative functions.
- Uses of medical records for research include evaluating effectiveness and adverse effects of treatment, monitoring care, identifying patients at risk of disease, monitoring population health, and developing policy.
- Although medical records research is more cost-effective than other types of research, it is important that researchers understand the limitations of the data and the obstacles for gathering such data.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of the role of paper and electronic medical records.
- General knowledge of pathophysiology and treatment of the following conditions: adolescent depression, pediatric obesity, pediatric asthma, and pediatric congestive heart failure.
- General knowledge of research design regarding: cohort, case-control, longitudinal design.

[Table of common pediatric laboratory reference values.](#)

ADDITIONAL READINGS

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Pennington AF, Strickland MJ, Freedle KA, et al. [Evaluating early-life asthma definitions as a marker for subsequent asthma in an electronic medical record setting.](#) Pediatr Allergy Immunol 2016;27:591-6.

Ventura ML, Battan AM, Zorloni C, et al. [The electronic medical record: pros and cons.](#) J Matern Fetal Neonatal Med 2011;24(suppl 1):163-6.

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Self-Assessment Questions

21. A researcher plans a study project using medical records research rather than claims databases. Which one of the following would be the most appropriate study for this researcher to conduct?

- A. Prescription use patterns for adolescents in the United States compared with Canada.
- B. Compliance of family practice physicians with screening for childhood obesity.
- C. Randomized controlled study of the efficacy and safety of clonidine compared with methadone for neonatal abstinence syndrome.
- D. Prescribing patterns of physicians compared with physician-extenders for infants presenting with otitis media in various counties throughout Nebraska, Kansas, and Iowa.

Questions 22–26 pertain to the following case.

P.T. is a pharmacist-researcher who plans to explore the use of inhaled steroids for moderate pediatric asthma at two large academic centers within the same community. The study would compare the effectiveness of early versus late initiation of inhaled steroids in the prevention of ED visits. P.T. reviews the literature to standardize the definitions of early and late initiation and plans to review records for the past 10 years. P.T. would like to include general pediatricians, pediatric pulmonologists, and family practitioners as the medical groups participating in the study.

22. Which one of the following is the best design for P.T.'s study?

- A. Prospective cohort.
- B. Case-control.
- C. Randomized controlled trial.
- D. Randomized cluster.

23. As P.T. begins to assemble the study, which one of the following is best as his first step?

- A. Present the study protocol to the institutional review board (IRB).
- B. Seek funding for the study from a pharmaceutical company.
- C. Discuss the study with the physicians representing each practice group.
- D. Begin collecting data within the electronic medical records (EMRs).

24. P.T.'s study begins. The three physician groups are employed by two different health care systems. Which one of the following is the greatest potential barrier to conducting P.T.'s study?

- A. Data-sharing policies between the two health care systems.

- B. Providers entering clinical information as free text.
- C. The physicians being employed by the two different health care systems.
- D. Missing data because the providers feel it is not clinically relevant.

25. Which one of the following components of the EMR would be best for P.T. to examine to study the outcome of interest?

- A. Results management.
- B. Electronic communication.
- C. Orders management.
- D. Patient support reports.

26. As P.T. begins collecting the information from the EMR, he encounters problems integrating the data fields between the two health care systems. One health care system uses EPIC EMR, and the other uses Cerner EMR. Which one of the following would be the most appropriate first step to take to resolve this issue?

- A. Limiting the study to one health care system.
- B. Contact an individual within the information technology (IT) department to ask for advice.
- C. Develop an abstraction and encryption system.
- D. Use a data warehouse where de-identified patient information would reside.

Questions 27–29 pertain to the following case.

The KidsFirst Hospital wants to improve its pediatric medication safety initiative. The hospital plans to implement two large programs: (1) barcode medication administration (BCMA) and (2) computerized physician order entry (CPOE). As the director of pharmacy, you have been asked to provide oversight of the performance improvement plan and possible publication of this KidsFirst Hospital initiative.

27. The KidsFirst Hospital leadership decides to implement the BCMA initiative first. Which one of the following is the most appropriate study design?

- A. Pre- and post-implementation cohort study.
- B. Case-control study.
- C. Randomized controlled study.
- D. Randomized cluster based on hospital floor.

28. The KidsFirst Hospital CPOE system includes a decision support tool that appears when the prescriber is ordering a medication. Which one of the following is the best example of a medical research study that could be done with implementing the KidsFirst CPOE decision-support tool?

- A. Rates of illegible prescriptions before and after implementing CPOE.
- B. Association of vancomycin-induced nephrotoxicity with patients who are receiving concomitant ibuprofen.

- C. Orders for opioid withdrawal scoring systems while decreasing the fentanyl infusion in patients within the pediatric ICU (PICU).
 - D. Rates of indomethacin-induced nephrotoxicity in neonates treated for patent ductus arteriosus.
29. The KidsFirst inpatient CPOE system has now been implemented for 3 years. Despite its overall success, some practice areas within the ambulatory clinics would prefer not to participate because of time constraints. This is very troubling to the CEO, and the director of pharmacy is asked to fix the problem. Both the CEO and the clinic physicians would like to use “science” to support their position. Which one of the following is the best strategy for the KidsFirst director of pharmacy to recommend?
- A. Conduct a study reviewing the outcomes of patients with the same ICD codes with physicians who use and do not use CPOE.
 - B. Conduct an online physician satisfaction survey comparing the inpatient physicians and the ambulatory physicians.
 - C. Randomly assign inpatient and ambulatory physicians to use either CPOE or paper orders, and assess prescribing errors.
 - D. Conduct a study evaluating the number of times that inpatient physicians “override” the decision support tools within the CPOE system.
30. A pharmacist wants to examine the relationship between medication errors, patient acuity, and pharmacist staffing ratios on a hematology/oncology floor. The pharmacist is concerned that the increased acuity of this patient population over the past 2 years places them at greater risk of a medication error when clinical pharmacists are not rounding on the floor. As the pharmacist begins to assemble the study, which one of the following would be the best initial step?
- A. Present the study protocol to the IRB.
 - B. Ensure the coordination between clinical, administrative, and information systems in the EMR.
 - C. Discuss the study with physicians representing each practice group.
 - D. Use a data warehouse registry to collect the de-identifiable information.

Learner Chapter Evaluation: Guidelines Review: Medical Records Research.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

36. The content of the chapter met my educational needs.
37. The content of the chapter satisfied my expectations.
38. The author presented the chapter content effectively.
39. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
40. The content of the chapter was objective and balanced.
41. The content of the chapter is free of bias, promotion, and advertisement of commercial products.
42. The content of the chapter was useful to me.
43. The teaching and learning methods used in the chapter were effective.
44. The active learning methods used in the chapter were effective.
45. The learning assessment activities used in the chapter were effective.
46. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

47. Classify the elements and functions of the medical record.
48. Apply real-world data to clinical research methods.
49. Analyze the strengths and weaknesses associated with medical records research.
50. Assess examples of pediatric-specific medical records research.
51. Please provide any specific comments related to any perceptions of bias, promotion, or advertisement of commercial products.
52. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

Questions 53–55 apply to the entire learning module.

53. How long did it take you to read the instructional materials in this module?
54. How long did it take you to read and answer the assessment questions in this module?
55. Please provide any additional comments you may have regarding this module:

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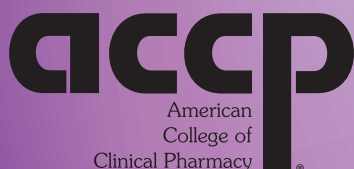
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<i>Immunology</i>	May 16, 2016	September 15, 2016	May 14, 2019
<i>Pediatric Critical Care</i>	September 15, 2016	January 17, 2017	September 14, 2019
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